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ORIGINAL ARTICLES

VACCINATION OF CHILDREN WITH VARIOUS CHORIOALLANTOIC PASSAGES OF MEASLES VIRUS

A Follow-up Study

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INTRODUCTION

EVIDENCE was presented in previous reports[1, 2] that: (a) blood or nasopharyngeal washings from children with measles would produce measles in the macaca mulatta; (b) measles virus could be grown on the chick chorioallantoic membrane in successive passages, and such passage virus could produce mild measles in the monkey; (c) certain monkeys developing typical mild measles from passage virus were subsequently resistant to challenge with active virus from human measles, and (d) such passage virus could produce mild measles with typical Koplik spots in small groups of susceptible children.

The resistance of a few children inoculated with passage virus was subsequently tested both by natural exposure in epidemics of measles and planned exposure, together with suitable control susceptibles, to active measles virus. The results obtained in these few children already reported[3] were sufficiently encouraging to suggest that fairly extensive field studies on the value of attenuated passage virus as a possible protective vaccine against measles should be carried out. The present report presents a brief outline of the findings in these field studies.

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Method of Study

At present, a field study on measles for the purpose outlined above has certain advantages over such studies of many other infectious diseases, but also certain disadvantages which greatly increase

TABLE I

Results of Inoculations in Monkeys

Strain	Material	Results Obtained on	
		Original Inoculation	Challenge Inoculation
PB-II	Blood	4 Positive	1 Negative 3 No challenge
PB-II	5th Chorioallantoic	? Positive	Positive
PB-II	16th Chorioallantoic	Positive	No challenge
PB-II	20th Chorioallantoic	Negative	No challenge
PB-IV	Blood	Positive	Negative
PB-IV	22nd Chorioallantoic	Positive	No challenge
PB-IV	39th Chorioallantoic	? Positive	No challenge
PB-IV	40th Chorioallantoic	Positive	Negative
PB-IV	80th Chorioallantoic	Positive	Positive*
PB-IV	91st Chorioallantoic	Positive	Positive*
PB-IV	103rd Chorioallantoic	Positive	Positive*
PB-IV	130th Chorioallantoic	Negative	Positive*
PB-IV	10th Allantoic fluid	Positive	Negative*
PB-IV	22nd Allantoic fluid	Negative	Positive
PB-X	3rd Chorioallantoic	2 Positive	2 Negative
PB-X	5th Chorioallantoic	Positive	Negative
PB-X	25th Chorioallantoic	Positive	No challenge
PB-XI	Blood	6 Positive	1 Negative 5 No challenge
PB-XI	3rd Chorioallantoic	2 Positive	1 Negative 1 No challenge
PB-IX	5th Chorioallantoic	1 Negative 1 Positive	2 No challenge
PB-XI	2nd Allantoic fluid	Positive	No challenge
PB-XI	3rd Allantoic fluid	Positive	Negative
PB-XI	2nd Allantoic fluid from 2nd chorioallantoic	Negative	No challenge
PB-XI	4th Allantoic fluid from 2nd chorioallantoic	Negative	No challenge

* All these monkeys received PB-XI blood as challenge inoculum.

the difficulty of obtaining conclusive data. The obvious advantages are three (1) approximately 98% of the population of the United States contracts frank measles at least once in the life span; (2) measles possesses a pathognomonic sign, the Koplik spot, which is a great diagnostic aid; (3) measles shares the distinction with such diseases as varicella and variola of being one of the most readily transmissible of all infectious diseases. The great disadvantage of measles for such field studies, how-

ever, lies in the lack, up to the present time, of suitable skin or serologic tests for susceptibility and immunity, despite repeated attempts to develop such tests.

At least, the advantages mentioned are of considerable assistance when possible resistance to measles as a result of vaccination is to be tested in the field. For purposes of the study, therefore, groups of children were selected, both from institutions, such as schools with considerable aggregations of susceptibles, as well as from homes where susceptible siblings could be followed as controls to the vaccinated children. The study was divided between two cities, Baltimore and Philadelphia. In Baltimore, where the investigation was supervised by one of the authors (S.S.G.) and a public health nurse, children were selected chiefly from the Eastern Health District. A nursery day school whose children could be followed closely was also selected. In Philadelphia, the children selected were spread somewhat more extensively among private families, schools and other institutions.

The children were inoculated with suspensions of chorioallantoic membrane of various passages, in accordance with the methods previously described[3,4] (*i.e.*, by the subcutaneous, intradermal or intranasal route). They were examined daily throughout the possible incubation period by the public health nurse and the physician for evidence of early malaise, coryza, conjunctivitis, fever, Koplik spots, or cough, and later, in addition, for evidence of rash. Chance epidemics of measles which occurred in later months were closely followed wherever possible in institutions whose children had been inoculated.

A preliminary statement on these studies has appeared elsewhere.[5]

Material

The virus passages on chorioallantoic membrane used for inoculation of the children ranged from the 4th to the 108th, and included 4 strains of measles virus, designated as PB-II, PB-IV, PB-X and PB-XI.

The data outlined in Table I indicate the reactions of monkeys (macaca mulatta) to inoculations with 4 of these strains of virus. Not only do they show the response of the inoculated monkeys to the material of different passages but, in most instances, the same monkeys' later response to challenge by active measles virus from human measles. It will be noted that the 5th passage of virus strain PB-II produced questionable measles in a single monkey and on subsequent challenge this animal was susceptible. Unfortunately, owing to the inability to obtain monkeys to use as controls, there was no challenge of the monkeys reacting positively to the 16th passage of PB-II virus. The evidence did not indicate that the virus of PB-II strain was transmitted so far as the 20th passage.

The inability to obtain monkeys for challenge studies at the time they were most needed was particularly unfortunate in the case of strain PB-IV, inasmuch as various chorioallantoic passages of this strain were used in most of the human inoculations. Its selection for the human studies was based upon the apparent production of mild measles in monkeys from inoculations of the 22nd, the 40th, the 80th, the 91st and the 103rd chorioallantoic passages. While the monkeys inoculated with virus of the 22nd or 39th passage were not challenged, owing to their death while being held, the monkeys inoculated with virus of passages 80, 91 and 103 all developed measles on challenge, thus indicating that none of the chorioallantoic passages subsequent at least to the 40th had produced resistance. The inability to obtain monkeys until too late thus obscured the value for the human studies of the various passages of this strain at the time the inoculations were carried out.

The virus passage material consisting of suspensions of infected chorioallantoic membrane was used both for parenteral (subcutaneous and intradermal) and for intranasal (spray or drop method) inoculation in the children.

Results

The nursery day school group furnished the most adequate data from the Baltimore area. One hundred fifty-seven children with no history of measles were inoculated with various passages of measles virus ranging, as indicated in Table II, from the fifth to the 54th of strains PB-IV, PB-X, and PB-XI. None of these children showed unmistakable evidence of mild measles with Koplik spots, although some had coryza and conjunctivitis from the 8th to 16th days. It was uncertain whether these signs resulted from the inoculations, although the time of appearance and their absence in the controls suggested that

the inoculations were responsible for their presence. A smaller group of 26 children of similar ages, who were in intimate contact with the inoculated group at the time of the later occurrence of measles, served as controls. Of the 157 children inoculated, 46 either left the study group or were not exposed. Thus, 111 inoculated children remained.

TABLE II

CHILDREN VACCINATED IN BALTIMORE

Strain and Passage of Virus	Number of Children	Signs of Take	Measles	No Measles	Average Interval in Days Between Inoculation and Rubeola	Not Exposed or Left Project
PB-IV-49th	6	0	4	2	230.7	0
	6	0	2	4	157.5	0
PB-IV-50th	6	0	1	1	165	4
	6	0	1	1	165	4
PB-IV-51st	2	0	2	0	317	0
	2	0	0	2	>60.0	0
PB-IV-54th	6	0	3	1	316.3	2
	6	0	0	4	>60.0	2
PB-X-5th	10	0	5	1	10.3	4
	24	0	21	2	32.3	1
PB-X-8th	3	0	2	1	35	0
	3	0	2	1	35	0
PB-XI-5th	12	0	6	0	12.8	6
	16	0	12	0	42.1	4
PB-XI-5th	9	0	6	0	9	3
	11	0	6	1	33.3	4
PB-XI-5th	13	0	5	2	19.4	6
PB-XI-5th	5	0	0	2	>60.0	3
	5	0	0	2	>60.0	3
PB-XI-14th	3	0	3	0	312	0
	3	0	0	3	>60.0	0
Totals	157	0	81	30		46
Controls	37		24	2		11

It will be noted that 17 of the children (in two groups of six children each and one group of five) contracted measles within 14 days from the date of their inoculation, while only one child of these three groups escaped the disease. Such a high incidence is similar to that of the control uninoculated children in whom 24 of 26 children, or 94%, contracted the disease when exposed under the same epidemic conditions at the nursery day school. In the above 18 inoculated children, measles was contracted by the 17 above-

mentioned children too early for any conceivable production of resistance by means of the passage measles virus in the inoculum. If these three groups (18 in all) are properly excluded, 64 children or 69% of the remaining 93 inoculated children contracted measles when they were exposed at later dates, as indicated in Table II.

TABLE III

CHILDREN VACCINATED IN PHILADELPHIA

Strain and Passage of Virus	Number of Children	Measles	No Measles
PB- II- 10th	3	1	2
PB- II- 26th	4	4	0
PB-IV- 7th	4	4	0
PB-IV- 30th	11	8	3
PB-IV- 35th & 36th	23	19	4
PB-IV- 40th	15	10	5
PB-IV- 52nd	11	7	4
PB-IV- 52nd & 55th	3	1	2
PB-IV- 53rd	19	18	1
PB-IV- 54th	3	2	1
PB-IV- 56th	1	1	0
PB-IV- 65th	7	2	5
PB-IV- 66th	12	8	4
PB-IV- 67th	6	6	0
PB-IV- 68th	12	8	4
PB-IV- 70th	6	4	2
PB-IV- 88th	11	10	1
PB-IV-101st	2	1	1
PB-IV-103rd	37	20	17
PB-IV-104th	53	32	21
PB-IV-105th	75	52	23
PB-IV-106th	48	35	13
PB-IV-108th	13	9	4
PB- X- 5th	1	1	0
PB-X-5+XI-15th*	1	0	1
PB-X-9+X-15th*	2	1	1
PB-XI-15th	3	2	1
Total	386	266	120
Controls	24	20	4

* In the first instance, two passages of the same virus strain and, in the second instance, different passages of different virus strains were mixed for the inoculum. The second mixture of PB-X-5th and PB-XI-15th is included under both strains in Table IV.

Although the numbers are small when the children are separated into groups according to the strain of virus used for their inoculum, it is of interest that as many as 15 children of the 28 inoculated with strain PB-IV escaped the disease, while only 10 of 36 children inoculated with strain PB-XI and only 4 of 29 inoculated with strain PB-X escaped measles.

Following the inoculations of 779 children in the Eastern Health District, unmistakable Koplik spots with mild measles appeared in only three children. It is, of course, possible

that in these cases the mild measles which occurred may have been derived from some other source. In a large number there were other symptoms from the 8th to 16th days, which suggested mild measles, but by far the major portion of the inoculated group had no respiratory symptoms. It was not found possible to conduct a follow-up study of this group either during the period of World War II or afterwards. For these reasons, this group of children is omitted from consideration in the present report.

In the Philadelphia area, of the 883 children inoculated originally in the study, it was found possible to follow 386, or 44%. Of the number followed, 266, or 69%, had contracted measles under home exposure or under environmental conditions in general equivalent to home exposure, while the remainder, 120 children, or 31%, had escaped the disease. In Table III are shown the groups of children divided according to the virus passage and strain used. Of a small group of 24 control children of similar age who were injected with normal allantoic fluid and similarly exposed to measles, 20, or 83%, developed the disease. Of a group of 44 children under 4½ years, all in intimate contact in one institution, 34 were inoculated, while 10 remained as controls. The negative history for measles appeared questionable in one of the 10 controls who, although heavily exposed on several occasions, did not develop the disease. Of the remaining 43 children, all eventually developed measles more than two weeks after inoculation. In these inoculated children, the vaccine had been administered both intradermally and by inhalation.

The interval between inoculation and the onset of measles as a result of later exposure was from 4 to 21 months, with an average of 12½ months. The severity of the disease when related to mean height and length of fever was considerably lower in the inoculated group, but the number of controls was actually too small for proper comparison. The fact that all 43 children developed measles indicates either that any resistance which may have been produced by the passage virus was minimal, or possibly that this exposure, *i.e.*, virus dosage, overwhelmed whatever slight resistance may have been present.

Discussion

The earlier small groups of children inoculated with early passage virus in the Philadelphia area unfortunately separated to a great extent, and most of them could not be traced. The largest and most important of these, which comprised 11 children from an orphanage, who were intimately exposed to measles in school and apparently resisted the disease, were all dispersed when the orphanage unexpectedly disbanded, and no trace of them could be obtained. The early passage virus in a considerable number of children of such earlier studies produced frank Koplik spots, a few maculo-papules on the skin, respiratory symptoms and slight fever, and in such instances, resistance to later infection with measles sufficient to either prevent or modify the disease apparently occurred, as indicated in the previous report.[4]

Among the remaining 17 children in the previous study[4] who escaped measles, there was only one (E.S.) who could be followed continuously up to the time of the present report. In response to her original inoculation with passage virus, and after a time interval commensurate with the usual incubation period of measles, she had shown Koplik spots, fever, coryza, conjunctivitis and a few macules. Also, her nasopharyngeal washings at that time produced typical measles in a monkey, thus fully confirming the activity of the passage virus. Since that time she has been intimately exposed on at least two occasions to measles, during severe epidemics in Philadelphia, without contracting the disease.

In Table IV are arranged, according to virus strain used, the number and percentages of inoculated children who escaped measles at the time of later exposure among those followed in both Baltimore and Philadelphia, together with the control groups from both urban areas. In the largest group of children combined from both areas who were inoculated with strain PB-IV, 130 of 400 children, or 32.5%, escaped measles on later exposure. It is of particular interest that in one of the most closely followed groups of children inoculated with this strain in the nursery day school, 15 of 28 children, or 54%, failed to develop measles.

In consideration of the data presented above, it must be stated that the results are somewhat inconclusive. When all of the information both from Philadelphia and from Baltimore is pooled together, and the validity of such pooling is suggested by the data presented in Table IV, it will be seen that of 479 children* inoculated and followed in the present study, 330, or 69%, developed measles. This figure should be compared with the 39% developing measles in those smaller groups of children, the study of whom formed a previous report.[3, 4] In the present series the control cases were few in number, totalling only 50, of whom 44, or 88%, developed measles. While the morbidity rate of 69% in the present series of inoculated children may be accepted as correct because of the number involved, for the same reason neither the 88% in the control series nor the 39% in the previous series can be given equal weight in attempting to assess the significance of the present studies. It is to be regretted that the onset of World War II interrupted these studies shortly after they had been initiated. It was for this reason that so many of the vaccinated children were lost from the study, and also that a larger series of control uninoculated children was not available.

TABLE IV

NUMBER AND PER CENT OF INOCULATED CHILDREN AND OF CONTROLS WHO COULD BE FOLLOWED AND WHO ESCAPED MEASLES TABULATED ACCORDING TO STRAIN OF VIRUS USED AND TO GEOGRAPHIC LOCATION

Strain of Measles Virus	Baltimore	Philadelphia	Total	Per Cent (total)
PB-II		2/7	2.7	29
PB-IV	15/28	115/372	130/400	32.5
PB-X	4/29	2/4	6/33	18
PB-XI	10/36	2/4	12/40	30
Controls (No Vaccine)	2/26	4/24	6/50	12

Numerator = number of children who escaped measles.
Denominator = total number of children in each group.
The inoculum for one child includes 2 strains, as indicated in footnote on Table III. Eighteen children included in Table II are omitted from Table IV because measles was contracted too early for any conceivable production of resistance by means of the passage measles virus in the inoculum.

SUMMARY

An extensive study of the usefulness of a vaccine produced by the growth of the measles virus on the chorioallantoic membrane of the fertile hen's egg was under-

* Eighteen children were omitted for reasons outlined under Table IV.

taken as a joint study in Baltimore and Philadelphia. Four hundred ninety-seven children were vaccinated and followed for a period covering at least one close exposure to a major epidemic of measles. Eighteen of these children contracted measles within 13 days of their vaccination, and thus could not be included in final tabulations. Of the remaining 479 children, 330, or 69%, contracted the disease. Fifty unvaccinated children served as controls and of these, 44, or 88%, developed measles. The morbidity rate of 69% of the present series should be compared with the morbidity rate of 39% in a smaller series of vaccinated children described by some of the present authors elsewhere. Although the present study suffered from certain shortcomings, it is believed that the following conclusions can be drawn. First, that the chorioallantoic membrane vaccine produced mild symptoms of measles in a large number but not in the majority of children vaccinated, and second, that whatever protection was afforded by the vaccination procedure was minimal in degree. Unfortunately, the reasons for the failure of the vaccine to afford better protection are not evident, nor does it seem probable that they will be fully understood until better methods are available for working with the virus *in vitro* and in the laboratory.

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Spanish Abstract

Vacuna de Niños con Varios Pasajes Corioalantoicos de Virus de Sarampión—Un Estudio Continuado

Se ha llevado a cabo un extenso estudio de la utilidad de una vacuna producida por el desarrollo del virus del sarampión en la membrana corioalantoica del huevo de gallina fértil. Cuatrocientos noventa y siete niños fueron vacunados y vigilados por un período abarcando por lo menos una exposición cerca a una epidemia grande de sarampión. Dieciocho de estos niños contrajeron sarampión dentro de 13 días de su vacuna y no pudieron ser incluídos en los cálculos finales. De los 479 niños que quedaron, 330, o sea el 60% contrajeron la enfermedad. Cincuenta niños sin vacunar sirvieron como controles y de éstos, 44, o sea el 88% cogieron sarampión. El tipo de morbidad de 69% de las series actuales se debe comparar con el tipo de morbidad de 39% en una serie más pequeña de niños vacunados descrito en otra parte. Aunque el estudio actual tuvo ciertas faltas, se cree que se pueda llegar a las siguientes conclusiones. Primero, que la vacuna de la membrana corioalantoica produjo síntomas ligeros de sarampión en un gran número, pero no en la mayoría de los niños vacunados, y segundo, que cualquier protección proporcionada por la vacuna fué mínima en grado. Desgraciadamente no se ven las razones por las cuales la vacuna dejó de dar más protección, ni tampoco parece probable que se comprendan bien hasta que no se tengan mejores métodos para trabajar con el virus *in vitro* y en el laboratorio.

1740 Bainbridge St.

A NEW REPOSITORY PENICILLIN (A FORM OF AQUEOUS PENICILLIN G PROCAINE) IN INFANTS AND CHILDREN

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WITH the advent of the Romansky formula[1] in 1944, the search for an "ideal" repository penicillin has been intensified. Although the effectiveness of penicillin in beeswax-peanut oil mixture in the treatment of infections has been adequately proved,[2-7] the cumbersome aspects of administration of the material and the occurrence of significant reactions and sterile abscesses soon led to a search for different vehicles for the slow release of penicillin.

Cannon et al.,[8] studying various vegetable oils, reported assayable concentration of penicillin in a greater number of patients with the use of hydrogenated cottonseed oil (melting point 40° C.) than with the Romansky formula. Hirsch et al.[9] described a mixture of penicillin in beeswax and peanut oil which was fluid at room temperature and which gave assayable levels of penicillin in serum for 15 to 20 hours when used in dosage of 300,000 units.

Ory et al.,[10] using a penicillin in water-in-oil emulsion containing cholesterol-peanut oil mixture (Pendil), concluded that blood serum levels were not higher than those obtained with penicillin dissolved in saline solution. However, Kaufman[11] using the same material reported good clinical results in 167 cases of various types of infections.

Salivar et al.[12] in March, 1948, described the preparation and chemical properties of a new penicillin complex produced by combining procaine with penicillin G. This product was found to release penicillin slowly and appeared well suited for repository use. Herrell and his co-workers,[13] using a sesame oil suspension of procaine penicillin G (Duracillin), reported "adequate concentrations" of penicillin in blood serum for at least 24 hours. Sullivan et al.[14] using procaine penicillin G with cottonseed oil as the vehicle obtained assayable serum levels in 20 of 21 patients 24 hours after administration.

This report describes experience with a new repository penicillin. This product is an aqueous penicillin G procaine* which has 150,000 u. of penicillin per ml. of vehicle. The vehicle consists of 1% tragacanth, 0.5% sodium chloride and chlorobutanol as a preservative.

CLINICAL STUDIES

Clinical Plan—A total of 82 patients were included in this study. Of these, 49 were treated with daily injections in the outpatient department and 33 in the hospital. No patient was included in

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* Generously supplied by the Abbott Laboratories. Two lots of penicillin were used in this study: lot E-1138 and lot E-1185. In the former, the particle size on a relative weight basis was as follows: 60% from 5-29 μ, and 40% from 30-99 μ. In the latter, the distribution was 29.0% from 5-29 μ, and 71.0% from 30-99 μ.

this series who was critically ill. It was decided that a variety of diseases commonly encountered would be included in the study, in particular, those in which beta Str. hemolyticus was suspected or proved as the etiologic agent.

Since penicillin was usually given before a bacteriologic diagnosis was made, 37 cases of nonspecific etiology were included. Organisms considered pathogenic were (1) beta Str. hemolyticus, (2) Diplococcus pneumoniae, (3) Staph. aureus (in the case of the 3 abscesses included in the study).

Dosage.—An arbitrary dosage schedule was established as follows: Infants up to 1 yr., 11 mos. of age, 150,000 u. daily; children from 2 to 7 yrs., 11 mos., 300,000 u.; children over 8 yrs., 450,000 u. These doses of penicillin were contained in 1.0 ml., 2.0 ml. and 3.0 ml. of the vehicle, and were administered deep into the muscle of the upper outer quadrant of the buttocks. Alternate sides of the buttocks were used for successive injections.

TABLE I

FREQUENCY OF SIGNS AND SYMPTOMS

		Signs						Symptoms									
	No. Patients	Nasal	Pharyngeal	Ear	Lymph Nodes	Chest	Other Local Lesions	Anorexia	Cough	Coryza	Fever	Sore Throat	Malaise	Earache	Irritability	Nausea & Vomiting	Discharging Ear
Otitis media, supp.	10	1	1	10	—	—	—	2	1	—	4	—	1	3	2	1	7
Otitis media, nonsupp.	11	5	9	11	3	—	—	4	3	3	8	—	1	5	6	3	—
Scarlet fever	3	1	3	—	—	—	3	—	2	3	3	2	1	—	—	—	—
Acute tonsillitis	9	2	9	1	4	—	—	2	—	1	8	8	2	1	—	1	—
Nasopharyngitis	18	9	18	5	7	—	—	6	5	5	10	6	7	1	2	4	—
B. strep. carrier	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Dpn. carrier	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cervical adenitis	2	1	2	—	2	—	—	—	—	—	—	1	—	—	—	—	—
Bronchitis	9	3	4	1	—	9	—	3	6	4	7	—	—	1	4	1	—
Laryngo-tracheo-bronchitis	3	—	2	—	—	3	—	1	2	—	2	—	—	—	2	3	—
Bronchopneumonia	2	—	1	—	—	2	—	—	2	—	2	—	1	—	—	—	—
Pneumonia, lobar	1	—	—	—	—	1	—	—	—	—	1	—	—	—	—	1	—
Abscess	3	—	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—
Cellulitis	1	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—
Impetigo	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Stomatitis	1	—	—	—	—	—	1	—	—	—	1	—	—	—	1	1	—
Total	82																

Serum penicillin levels were obtained only on patients hospitalized.

Clinical Evaluation.—Clinical evaluation was based on daily examination of the patients at the time of injection. On the first examination, leukocyte and differential counts as well as cultures of the nose and throat, or of the discharge in the case of suppurative otitis media or abscess, were made. Cultures and blood counts were repeated during and at the end of penicillin treatment. Clinically, the results were graded as "good," "fair," "poor," and "unknown." Bacteriologically, they were judged "successful" or "unsuccessful," depending upon the elimination of the presumed offending organism during the course of treatment.

Clinical Results.—Table I gives the 16 clinical syndromes included in the study and the frequency

of the presenting signs and symptoms in each classification. The type of pathogens and the bacteriologic and clinical evaluation are given in Table II.

Table III shows the type of medication used prior to penicillin therapy and the duration of the illness after penicillin G procaine was instituted. Sulfonamides had been used unsuccessfully in 12 cases.

TABLE II

CORRELATION OF CLINICAL SYNDROMES WITH BACTERIOLOGIC AND CLINICAL RESULTS

		Cultures				Bact. Results		Clinical Results			
	No. Patients	No. Pathogens Identified	Str. Hem. Beta	Dpn.	Staph. Aur. Abscess	Successful	Unsuccessful	Good	Fair	Poor	Unknown
Otitis media, supp.	10	6	3	T1	—	4	—	10	—	—	—
Otitis media, nonsupp.	11	— 6	— 3	T6 T4	— —	— 4	1 —	— 10	— —	1 —	— —
Scarlet fever	3	—	3	—	—	3	—	3	—	—	—
Acute tonsillitis	9	4	5	—	—	5	—	7	—	2	—
Nasopharyngitis	18	10	8	—	—	8	—	15	—	—	3
B. Str. carrier	6	—	6	—	—	6	—	—	—	—	—
Dpn. carrier	2	— —	— —	T6 T29	— —	— 1	1 —	— —	— —	— —	— —
Cervical adenitis	2	—	2	—	—	2	—	2	—	—	—
Bronchitis	9	— 4 —	2 — —	T7 T23 T?	— — —	3 1 —	— — 1	3 5 —	— — 1	— — —	— — —
Laryngo-tracheo-bronchitis	3	2	—	T17	—	—	1	3	—	—	—
Bronchopneumonia	2	1	1	—	—	1	—	2	—	—	—
Pneumonia, lobar	1	—	—	T(1 & 9)	—	1	—	1	—	—	—
Abscess	3	—	—	—	3	—	—	3	—	—	—
Cellulitis	1	1	—	—	—	—	—	1	—	—	—
Impetigo	1	—	1	—	—	1	—	1	—	—	—
Stomatitis	1	—	1	—	—	1	—	1	—	—	—
Total	82	34	35	10	3	41	4	67	1	3	3

The age distribution of patients treated was as follows: 36 below 2 yrs., 37 from 2 to 7 yrs. and 11 mos., and 9 were 8 yrs. and over.

In every instance of infection with beta Str. hemolyticus (35 cases) the clinical and bacteriologic results were considered "good' and "successful," respectively. The distribution of the strains was: 18, group A; 1, group B; 4, group C; 1, group F, and 11, not groupable.

In the 3 cases of abscess, both the clinical and bacteriologic responses were satisfactory.

Less satisfactory results were obtained in the 10 cases where a pneumococcus was found. In the child with laryngo-tracheo-bronchitis, where pneumococcus type 17 was found in the pharynx, the clinical result was "good" but the organism continued to appear in subsequent cultures of the throat. In the case of suppurative otitis media from which pneumococcus type 6 was grown from the throat and the ear, the bacteriologic and clinical results were considered unsatisfactory. In the healthy carrier of pneumococcus type 6, the organism persisted in the throat in spite of the therapy. In the case of bronchitis from which an untypable pneumococcus was found in the pharynx, the bacteriologic result was considered "unsuccessful" and the clinical result "fair." In addition to the above results, there were 2 cases of tonsillitis of nonspecific etiology in which clinical results were considered "poor" and 3 cases of nonspecific nasopharyngitis in which clinical results were unknown.

TABLE III

NUMBER OF CASES WITH DURATION OF ILLNESS BEFORE AND AFTER TREATMENT

Days	Duration of Sulfonamide Therapy Before Penicillin G Procaine	Duration of Illness Before Penicillin G Procaine	Duration of Therapy with Penicillin G Procaine	Day First Negative Culture Obtained	Duration of Signs and Symptoms After Penicillin G Procaine Therapy Started
0	—	6	—	—	—
1	2	13	—	13	6
2	1	12	3	17	12
3	1	9	15	8	17
4	2	11	25	1	14
5	3	5	21	2	13
6	—	2	10	—	5
7	—	6	4	—	—
8	—	1	3	—	—
9	1	1	—	—	—
10	—	3	—	—	—
11	—	—	1	—	—
12	—	1	—	—	—
2 wks. and over	1	10	—	4	7*
Unknown	1	2	—	—	—
Total	12	82	82	45	74

* Of these, 1 was graded fair, 3 poor, and 3 unknown in the clinical evaluation.

Penicillin G procaine was given for 6 days or less to 74 of the patients (90%), while the remainder received it for a maximum period of 11 days. Of the 45 patients in whom a definite bacteriologic diagnosis was made, a bacteriologic cure was effected in 41 (91%) within 5 days, and in none was success obtained thereafter.* Clinical cures were obtained within 5 days in 62 of the 67 patients (93%) who were successfully treated.

Complications.—No instance of sterile abscess, local reaction, or sensitivity to the penicillin or the vehicle was observed.† At the beginning much difficulty was encountered with clogged needles, but during the course of study, as the experience of the administrators increased, it was largely overcome. It was found best to shake the solution vigorously and to use a needle no smaller than a No. 20 gauge.

* The 4 bacteriologic failures were all pneumococci discussed previously.

† A total of approximately 20,000 doses of aqueous penicillin G procaine (Abbott) have been administered to approximately 3,000 patients at the University of Chicago Clinics in a 6 mo. period. Only 1 reaction has been observed to date. This was a transient urticaria in an adult patient which responded to antihistamine therapy.

Blood Level Determinations

Method.—A modification of the technic described by Rammelkamp[15] was used for all penicillin blood level determinations. The standard organism employed was a strain of group A beta Str. hemolyticus, designated Cl4, which was isolated in this laboratory in 1946 from the throat of a patient with scarlet fever. This organism has maintained its penicillin sensitivity at a level of 0.008 u. penicillin/ml. of media when standardized at approximately bi-monthly intervals against standard penicillin G. A 10-tube technic was employed for all determinations. Each tube contained tryptose phosphate broth (Difco) plus 0.1% defibrinated sheep's blood, and 0.1% 18 hr. broth culture of the test organism. One half ml. of patient's serum was pipetted into the 1st tube and serial 2-fold dilutions were made through the 10th tube, using the same pipette for each transfer. Visible growth of flocculated organisms after 18 hrs. incubation at 37.5°C. was used as the end point.

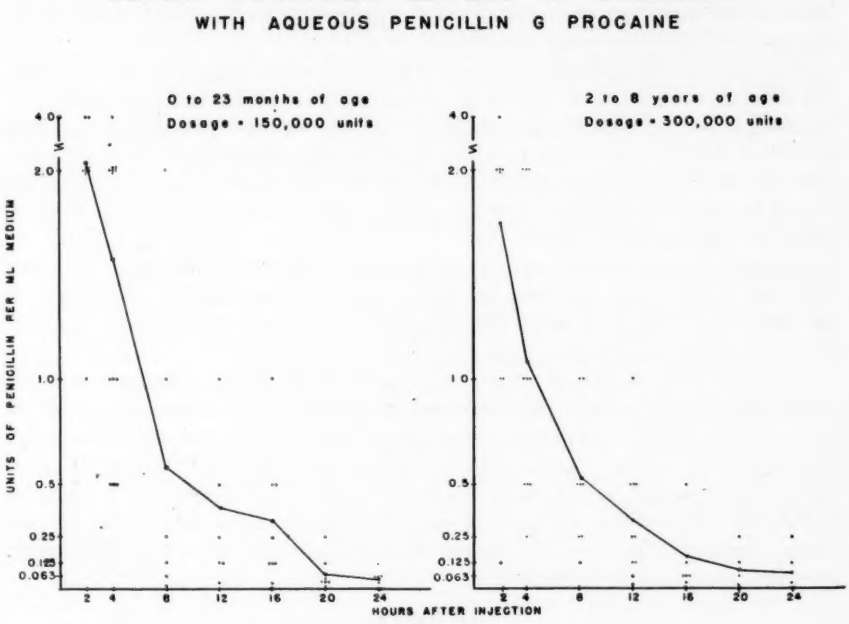

FIG. 1

Results.—A total of 48 patiencts who had received a daily dose of aqueous penicillin G procaine was studied. An average of 2.3 serum levels per patient was made on 25 patients under 2 yrs. of age, while 2.2 were performed on 23 patients from 2 to 8 yrs. of age. A maximum of 5 determinations per patient was made in either age group.

Graphs showing the serum levels in the younger and older age groups, respectively, are given in Figure 1. The curve of the mean values is represented as a solid line and the individual determinations as solid dots. It is evident that there is a wide range of values for a given hour. The trend, however, is constant for both age groups and the curves approximate a normal curve. In all instances the penicillin blood level was 0.25 u./ml., or less, 20 hrs. after the injection and in several children levels too low to be determined were observed at 20 or 24 hrs.

Penicillin Sensitivity of Streptococci

Twenty-seven strains of beta Str. hemolyticus obtained from patients in this study before penicillin therapy was started were tested for penicillin sensitivity by the ditch plate method of Fleming.[16] Of these strains, 14 were group A; 1, group B; 4, group C; 1, group F, and 7, ungroupable by the

Lancefield technic. The sensitivity range for groups A, C, and ungroupable organisms was 0.01 to 0.02 u./ml. of media. The single strains of group B and F were sensitive to 0.05 u./ml. of media. These are all interpreted as being within the normal range of sensitivity for streptococci.[17-19]

Discussion

The efficacy of aqueous penicillin G procaine in the treatment of various infectious diseases in children can only be suggested from these data. The limitations of this study are: 1. the relatively small number of patients in each of the clinical categories, and 2. the fact that all patients included were treated and none was left as control.

The most convincing evidence which suggests that this form of therapy is both useful and adequate is found in patients with beta Str. hemolyticus in the nasopharynx. In the 35 patients in whom this organism was isolated, clinical and bacteriologic success was obtained within three days. In no instance was a positive culture for beta Str. hemolyticus obtained after penicillin therapy was initiated.

The least convincing evidence is found in the group where no specific etiologic agent was demonstrated and where conclusions are based entirely upon the clinical impression. Inasmuch as most of these diseases are self limited, eventual cure would be expected with or without therapy. The criteria for effectiveness of daily repository penicillin, therefore, were: 1. shortening of the expected duration of the illness and 2. rapid change in the clinical picture with a decrease in the fever soon after treatment was started. These, of course, are both subjective criteria.

Aqueous preparations of penicillin G procaine have certain advantages over oily emulsions of the same salt. They are easy to administer, reactions or sensitization to the vehicle are unlikely to occur, the dangers of an oil embolus are absent and complications, such as sterile abscesses, are rare.

No attempt will be made to answer the question as to what is an adequate penicillin serum level. There would be little argument that levels, such as those observed in the first eight hours after a dose of aqueous penicillin G procaine, would be called "adequate." The levels obtained for the second 12 hours after an injection, where many of the values were 0.063 u./ml. or less, probably would not be considered "adequate" by some investigators. Although low blood levels existed during the latter half of the 24 hour period, therapeutic success was obtained in nearly all cases where penicillin might reasonably be expected to be effective.

Summary

Eighty-two children with a variety of infectious diseases were treated with a daily injection of a new repository penicillin, aqueous penicillin G procaine (Abbott).

Clinical success was obtained in 68 of 75 patients. In one, the results were considered fair, in three poor, and in three unknown.

Thirty-five patients had a beta Str. hemolyticus, and 10 a pneumococcus isolated from the nose or throat. Bacteriologic success was obtained in all streptococcal infections, but in only 6 of 10 pneumococcal infections.

All of the streptococci were sensitive to penicillin when tested by *in vitro* methods.

Penicillin serum levels with a mean maximum of approximately 2 u./ml. were observed at two hours, and mean minimum of approximately 0.063 u./ml. at 24 hours. The curve of intermediate values approximated a normal curve.

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SPANISH ABSTRACT

Una Nueva Penicilina Repositoria (Una Forma de Procaina de Penicilina G Acuosa) en Infantes y Niños

Ochenta y dos niños con una variedad de enfermedades infecciosas fueron tratados con una inyección diaria de una nueva penicilina repositoria, procaina de penicilina G acuosa (Abbott).

Se tuvo éxito clínico con 68 de 75 pacientes. En uno los resultados fueron considerados regulares, en tres, malos, y en tres, desconocidos.

Treinta y cinco pacientes tuvieron una beta Str. Hemolyticus, y 10 una penumococcus aislada de la nariz o garganta. El éxito bacteriológico se obtuvo en todas las infecciones estreptocócicas, pero solamente en 6 de 10 infecciones neumocócicas.

Todas las estreptocócicas fueron sensibles a la penicilina cuando ensayadas por métodos *in vitro*.

Las cantidades de suero de penicilina con un máximo medio de aproximadamente 2 ml. fueron observadas a las dos horas, y un mínimo medio de aproximadamente 0.063 u./ml. a las 24 horas. La curva de valores intermedios se aproximaron a una curva normal.

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CONGENITAL MYASTHENIA GRAVIS

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THE question as to whether myasthenia gravis is a hereditary or familial disease has been discussed in numerous publications. Most authorities hold that these factors do not play a part in the etiology, but that there may be a familial or genetic tendency as is suggested in the case presented here. Riley and Frocht[1] reported myasthenia gravis occurring in two sisters. Rothbart[2] reported two cases of the disease in brothers, one in whom the onset was in early infancy. Two other brothers in this same family also presented symptoms of myasthenia gravis. Bowman[3] listed one case of apparent congenital myasthenia gravis. Strickroot, Schaeffer and Burgo[4] presented the case of a myasthenic mother with a newborn son who also exhibited symptoms of myasthenia gravis which were abated by the action of prostigmin. Hart[5] described myasthenia gravis with ophthalmoplegia and constitutional anomalies in sisters. Marinesco[6] noted the condition in two sisters.

This is a case of an infant who showed symptoms at birth, and can be added to the reported cases of familial incidence which suggest possible hereditary aspects.

CASE PRESENTATION

The mother of this infant is a known patient with myasthenia gravis which has been controlled for the past 2 yrs. with prostigmin therapy. The infant was delivered at Provident Hospital.

First day of life: Physical examination at birth revealed a fairly well developed Negro male, wt. 3135 gm., with polydactylism consisting of extra little fingers, which were ligated. Second day: Baby appeared listless. Third day: Wt. 2895 gm. Formula was taken but only over a prolonged period of time. A Breck feeder was tried, but he regurgitated feedings. Hands appeared slightly large but were believed normal. Fourth day: Only a small portion of the feeding was taken and this with difficulty. Infant developed a physiologic jaundice and became slightly dehydrated. There seemed to be slight relaxation of lower jaw.

Fifth day: All feedings were taken poorly. Child developed slight ptosis of right eyelid and, seemingly, a pseudoparalysis of lower jaw. He was inactive and cry was weak. There was little movement of the facial muscles. Skin was dry; heart and lungs were essentially negative.

Seventh day: Wt. 3045 gm. Infant received the prostigmin test. Prostigmin 0.00375 gm. was given by gavage in 30 cc. of formula. Regular formula was offered 30 min. later and taken well. Within this 30 min. period, ptosis of the eyelid disappeared, cry became stronger and the infant seemed to become more active. He was placed on a maintenance dose of prostigmin bromide 2 mg. q. 4 h. Subsequent feedings were taken normally, and the signs listed previously did not reappear.

The infant was taken off prostigmin therapy on the 9th day of life. Twelve hrs. later, he took the formula with difficulty and cry became feeble. Prostigmin therapy was started again and all symptoms abated as before.

He was taken off prostigmin again 2 days later. He was still feeding normally 17 hrs. after prostigmin was stopped, but 24 hrs. after the discontinuance, he showed signs of poor sucking power and feedings became difficult. Thirty-nine hours after prostigmin had been discontinued, cry was feeble, there was a ptosis of the right eyelid and sucking power was extremely poor. When he was placed back on prostigmin therapy, all symptoms again disappeared. (See Figures 1-4.)

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Whenever prostigmin therapy was resumed, the dosage for the initial dose was doubled (4 mg.) At no time during this period of hospitalization did the infant develop a diarrhea or show signs of hyperperistalsis resulting from the prostigmin medication.

Five drops of "Vi-penta" were given daily after the 10th day.

Blood and urine examinations were essentially negative. Rh factor was negative. Roentgenogram at 1 mo. of age showed a wide supracardiac shadow suggestive of a large thymus (Figure 5). However, no radium therapy was given.

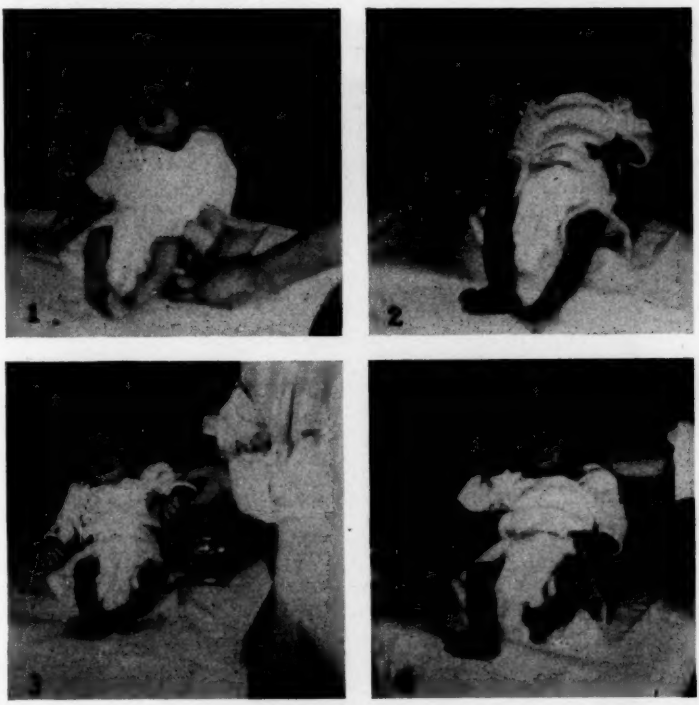

FIG. 1. Infant before prostigmin administration. Note general listlessness and drooping right eyelid.
FIG. 2. Infant 10 min. after prostigmin administration.
FIG. 3. Infant 20 min. after prostigmin administration.
FIG. 4. Infant 30 min. after prostigmin administration.

The infant was discharged from the hospital weighing 3135 gm. A maintenance dose of prostigmin bromide 15 mg. was ordered given in the daily formula.

The child returned to the hospital for a circumcision at the age of 4 mos. He was still receiving his daily medication and appeared to be a normal baby. He was active and there was no ptosis of the lid, weakness in the sucking reflex, or pseudoparalysis of the lower jaw. Cry was vigorous and reflexes physiologic.

DISCUSSION

Myasthenia gravis is characterized by a disturbance of the chemical components present at the myoneural junctures of certain muscles. The substances involved are acetylcholine, which is liberated from the terminals of motor nerves and serves as a transmitter of impulses to the muscle fibers, and the enzyme cholinesterase. This enzyme is found in the blood serum and tissues of the body but, according to Marnay and Nachmansohn,[7]

it is found in greater proportion in the muscular motor plate than in the rest of the muscle.

Goñi[8] states that the acetylcholine liberated is immediately destroyed by cholinesterase which hydrolizes it into acetic acid and choline.

It is believed that in myasthenia gravis there is either a deficit of the liberated acetylcholine or an excess of cholinesterase present. In either case the transmission of impulses is interrupted and a condition simulating muscular paralysis results. These symptoms are relieved by the action of parasympathomimetic drugs such as prostigmin

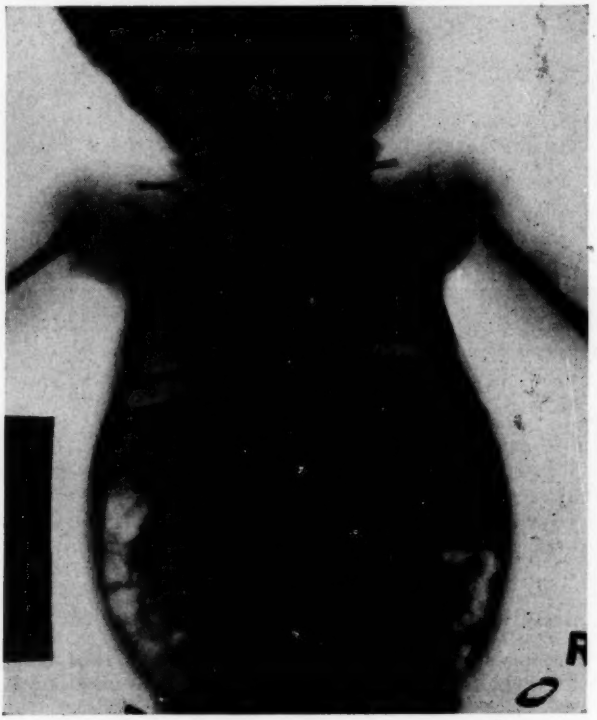

FIG. 5. Supracardiac shadow suggestive of enlarged thymus.

and physostigmine which inhibit the action of cholinesterase and permit the accumulation of acetylcholine at the myoneural junction.

Yahr and Davis[9] mentioned the fact that muscle potassium concentration, which plays a role in muscular contraction, is increased in myasthenia gravis, and the degree of muscle weakness appears to be associated with the amount of potassium in the muscle at the time. They also state that the administration of prostigmin which relieves the weakness causes a decrease of the muscle potassium level. There is then a corresponding increase in blood potassium.

Investigation has shown frequent occurrence of adenoma or hypertrophy of the thymus in individuals with myasthenia gravis, and surgical extirpation of the thymus has been

suggested in such cases. Blalock and collaborators[10] show a remission of symptoms after five out of six such operations. Goñi[11] believes that roentgen therapy on the thymus should be tried on most myasthenics since shock and risk are less than that involved in surgery.

Myasthenia gravis is expressed clinically by an easy fatigue in certain muscles that seem to recuperate after variable periods of rest.

Early symptoms of the disease may be a general listlessness and, in children, the inability to keep pace with the play of other children. The first objective sign in most cases involves the oculo-labio-laryngeal orbit. These signs vary according to which muscles are affected, but there is usually a ptosis or drooping of one or both eyelids. The muscles of mastication are next involved, and there occurs an expression of sadness on the face. At the beginning of a meal chewing is easy, but it soon becomes difficult as the mucles become fatigued. The lower jaw hangs and the mouth sags; in some instances there is drooling. These patients try to stabilize the lower lip by holding it with the upper teeth, as has been noted by Goñi and Lanari.[12] Pharyngeal and laryngeal muscles are also affected. The patient has difficulty in swallowing, and vocal changes are present. There may be regurgitation of food in infants and children, and the cry becomes weak and feeble.

The legs are frequently involved; the patient seems awkward and often falls. There is inability to climb stairs or walk any considerable distance.

Other muscles of the body may be affected occasionally, but those mentioned here are the ones usually involved.

Prostigmin is the drug most frequently used in treating this disease, and results obtained from this therapy have been spectacular. It is given orally and parenterally, and the dosage varies with the duration of the effect of the medication.

Other drugs used successfully in treating this condition and as listed by Goñi[13] are ephedrine, potassium, guanidine, glycocol, choline, and veratrine.

The administration of these drugs, especially prostigmin, aids in the differential diagnosis of myasthenia gravis, and the response to prostigmin establishes the diagnosis without a question.

In severe amyotonia congenitia the deep reflexes are absent and prostigmin produces no obvious improvement in power. Further, in amyotonia congenitia ptosis of the eyelid is no part of the clinical picture. In progressive bulbar paralysis there is atrophy of the tongue and lips which is absent in myasthenia. Progressive muscular dystrophy is characterized by atrophies of distinct muscle groups. Bulbar tumors show affections of the sensory pyramidal paths, and these symptoms are usually unilateral. Lateral amyotrophic sclerosis, traumatic neuritis, and alcoholic neuritis along with the conditions listed above will not respond to prostigmin therapy. The same is true of injury to the cervical cord at birth. Also, in this condition there is no ptosis or any defect above the level of the cranial nuclei in the pons.

Conclusion

A case of congenital myasthenia gravis has been presented. Familial and possible hereditary cases of this disease previously reported have been listed, and a short discussion of the disease presented.

No definite statement can be made that myasthenia gravis is hereditary or familial, but this case and those previously reported indicate familial and possible hereditary aspects.

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13. Goñi,[8] pp. 57-64.

SPANISH ABSTRACT

Miastenia Gravis Congénita

Se presenta una caso de un infante con miastenia que nació de una madre con mistenia gravis. Este infante pareció indiferente el segundo día de vida, regurgitó los alimentos, mostró una relajación ligera y seudoparálisis del maxilar inferior, se le cayó el párpado derecho, lloraba suave, y quedó sin actividad al quinto día. Los roentgenogramas mostraron una sombra ancha supracardíaca sugestiva de un timo grande (el que se encuentra presente en muchos casos de miastenia gravis).

Se le dió 3.75 mg. de bromuro prostigmina por gavaje. Treinta minutos más tarde todos los síntomas mencionados arriba habían disminuído y el niño reaccionó normalmente. Colocado en una dosis de 2 mg. de bromuro prostigmina cada cuatro horas, quedó asintomático todo el tiempo que los medicamentos continuaron. Los síntomas miasténicos volvieron a parecer cuando la terapia cesó.

Esta enfermedad está caracterizada por un desorden de la relación química que existe entre la acetilcolina y el enzima colinesterase en las coyunturas mioneurales de ciertos músculos, particularmente aquellos de órbita oculo-labio-laríngea. Se dice que los síntomas se alivian quirurgicamente mediante extirpación del timo, y medicamente mediante administración de medicinas parasimpatomiméticas, tales como la postigigmina y la fisostigmina.

Este caso y otros que se han relatado anteriormente indican posibles aspectos familiares hereditarios en la miastenia gravis.

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BRONCHIECTASIS IN CHILDHOOD

I. Clinical Survey of 160 Cases

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AS THE aetiology of bronchiectasis becomes more clearly understood, it should be possible to prevent this disease in many cases. Furthermore, with the development of surgical technic, a cure can be offered to an increasing number of patients. Knowledge of the development and progress of the disease, however, is still inadequate, particularly in childhood, the age period during which most cases date their first symptoms. For this reason, a study of bronchiectasis in childhood has been undertaken. It commenced with an investigation of children with chronic chest complaints and from them were selected three groups: 1. those diagnosed as having irreversible bronchiectasis, 2. cases of pulmonary collapse and chronic or recurrent pneumonia, many of which showed reversible dilatation of the bronchi, and 3. cases of doubtful bronchiectasis when first seen. It is from groups 2 and 3 that knowledge of the early stages of bronchiectasis developed. It was then realized that to assess the comparative value of medical and surgical treatment a long-term follow-up of cases should be carried out. A special aspect of this follow-up is the study of the compensatory changes that occur in remaining lung tissues of children after pulmonary resection.

The results of this work will be presented in three parts, the first only appearing in this issue; parts II and III will be published in later issues.

I. Clinical Survey of 160 Cases of Established Bronchiectasis.
II. Etiology and Pathogenesis of Bronchiectasis, with a study of 272 cases of pulmonary collapse and 99 cases of doubtful bronchiectasis.
III. Prophylaxis, Treatment and Prognosis, with a follow-up study of 202 cases of bronchiectasis.

* * *

"The organic lesion which I am now to notice, seems to have been hitherto entirely overlooked, both by the anatomist and the practitioner." These were the opening remarks by Laennec[1] in 1819, when he first described his pathologic discovery of dilatation of the bronchi. If the word "entirely" is replaced by "frequently," then his remarks would well apply to the present day. Until the introduction of iodized oil by Sicard and Forestier[2] (1922) to outline the bronchial tree, the diagnosis of bronchiectasis was usually made on autopsy material, or on the gross clinical picture. With improvement in bronchographic technic, however, it is becoming evident that many patients, previously diagnosed as suffering from chronic bronchitis, have in fact bronchiectasis confined to one or more segments of the lung. Treatment was largely palliative until the development of the one stage lobectomy by Brunn[3] (1929), which offered a cure to certain selective

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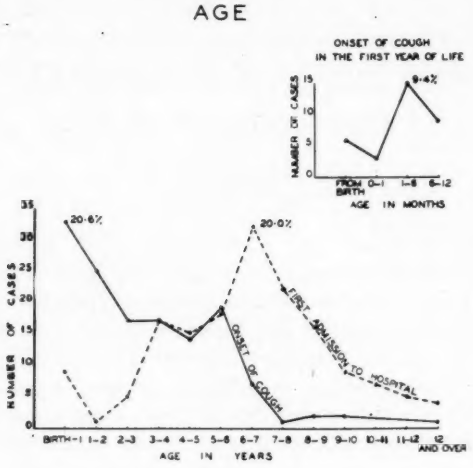

CHART 1

TABLES FOR CHART 1

AGE ON ADMISSION TO HOSPITAL

Age in years	0	1	2	3	4	5	6	7	8	9	10	11	12	Total
No. of cases	9	1	5	17	15	18	32	22	16	9	7	5	4	160
%	5.6	0.6	3.1	10.6	9.4	11.3	20.0	13.8	10.0	5.6	4.4	3.1	2.5	100

AGE OF ONSET OF COUGH

Age of onset in years	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–10	12–	No record	Total
No. of cases	33	25	17	17	14	19	7	1	2	2	1	22	160
Percentage	20.6	15.6	10.6	10.6	8.6	11.6	4.4	0.6	1.3	1.3	0.6	13.8	100

AGE OF ONSET IN FIRST YEAR

Age of onset in months	From birth	0–	1–	6–12	Total
Number of cases	6	3	15	9	33
Percentage	3.8	1.9	9.4	5.6	20.6

cases. Since then, rapid progress has been made both in surgery and anaesthesia, so that the operative mortality in children has been considerably reduced. Furthermore, selection of cases for operation now includes those with more extensive and widespread disease. This has recently been described by Pilcher,[4] who, using the technic of segmental resection, successfully operated on all five lobes of the lungs in one patient.

VITAL STATISTICS

The following information, supplied by Dr. Percy Stocks, Medical Statistician to the General Register Office of England and Wales, shows the inadequate data available on the mortality and morbidity of bronchiectasis. It has not been distinguished in the

International List of Causes of Death until, as a result of the drafting of proposals for revised classification, it was given a distinctive code number as from mid 1946. The most recent year for which any count of deaths attributed to this cause was made is 1927. In that year there were 10,969 deaths classed to International No. 99(b) Chronic bronchitis, and a sample of these showed that 5.3% were described as bronchiectasis (or its synonyms). The death rates in that year are estimated from this sample as:

Ages under 15 yrs. ..... 7 per million
Ages 15-64 yrs. .....15 per million
Ages 65 yrs. and over .....40 per million

As the patient usually dies from one of the complications of the disease, such as pneumonia, many cases will die incorrectly recorded, unless the diagnosis has been made during life, or at autopsy.

For morbidity, some limited figures are available for the two years 1942-43 when the proportionate morbidity rates per 1000 total illnesses (not violent causes) causing admission to Emergency Medical Service Hospitals of men and women from the services were as follows:

Bronchiectasis (No. 458 in the Medical Research Council Classification per 1000 total illnesses, 1942-43.)

Age group	*Men*	*Women*
18 yrs.	2.1	0.8
25 yrs.	1.7	
35 yrs.	1.9	—
45 yrs. and over	4.6	—

These groups were, of course, physically selected and rates based on a population at risk cannot be obtained at present. However, most incidence rates underestimate the true state of affairs, as the milder forms of bronchiectasis frequently pass unrecognized clinically.

Much of the confusion in diagnosis of bronchiectasis arises from inadequate definition. The word bronchiectasis has a Greek derivation, βρόγχος (bronchus) + ἔκτασις (dilatation), and means no more than dilation of the bronchus. Dilated bronchi, as observed by bronchography in children, frequently revert to normal calibre when the associated lung pathology clears so it is necessary to distinguish two types of bronchiectasis, reversible and irreversible. In practice it is important to differentiate these two types, as active medical treatment should be instituted until it seems inevitable that permanent irriversible pathologic changes have taken place in the bronchi, when surgical intervention can be considered.

Clinical Survey

The following records of 160 cases of irreversible bronchiectasis were compiled from children attending the outpatient department, or admitted to the wards of the Hospital for Sick Children and University College Hospital, London. No case was included in the series unless the diagnosis was confirmed by a bronchogram, or in 10 cases at autopsy, seven of these being in the first year of life. Separate chest records were kept of each case and as far as was possible personal questioning of the parents on each item in the

history was made. Patients were reviewed at a follow-up clinic at least once in six months and their progress has so far been observed for varying periods up to 10 years.

Sixty-seven cases occurred in males and 93 cases in females.

In Chart I the children are grouped according to their ages on first admission to hospital. The majority in the first year of life were of the fulminating type, proved at autopsy. A reluctance to perform bronchograms in the first three years of life may account for the low figures from one to three years. The large number in the six and seven year age groups probably coincides with increased contact with infection at school age, although closer observation of the child by teacher and doctor may account for some of the increase. The reduction after this age is noteworthy. It should be noted that the age of onset of cough is quite different.

TABLE I

CHARACTER OF COUGH

Cough	No. of Cases	Percentage
Constant	118	73.8
Intermittent	36	22.5
No record	6	3.8
Total	160	100

Cough (see Table I) was present or complained of in all. Its character varied considerably with the type of child and severity of the bronchiectasis. The parent was asked specifically if the cough was constantly present every day, or whether there were periods of freedom lasting several days or several weeks. If such was the case, the cough was described as intermittent.

It is noteworthy that in 73.8% of cases the cough was constantly present except perhaps on dry summer days.

The danger of permanent damage to the bronchi occurring in infancy is revealed in Chart 1. In 33 cases the cough originated in the first year of life and 24 of these started in the first six months; furthermore, 12 of the 22 cases with no definite date of onset were reported to have had a cough since infancy.

It will be noted from Chart 2 that in 56 cases (35%) symptoms were dated from an attack of pneumonia with or without an infectious disease, and in 48 cases (30%) from an attack of pertussis. Furthermore, in 18 of the 160 cases (11.3%) the pneumonia or pertussis occurred in the first year of life. Although a parent's history of these diseases may be inaccurate the figures are sufficiently imposing to suggest important predisposing factors. Rubeola, however, was less important, but the figures for asthma and "bronchitis" were significant; 20 cases (12½%) in all named these two conditions as the predisposing illness and most of these dated the onset to the first three years of life. However, both diseases are so commonly associated with other lung conditions, including bronchiectasis itself, that it was difficult to assess their real importance as a predisposing cause. The miscellaneous group included varicella, epidemic parotitis, pyelitis, nephritis, influenza, rubella, scarlet fever, nasal catarrh, polyp of the larynx and mechanical damage to the larynx. No case was attributed to a foreign body and none appeared to follow removal of tonsils and adenoids in this series.

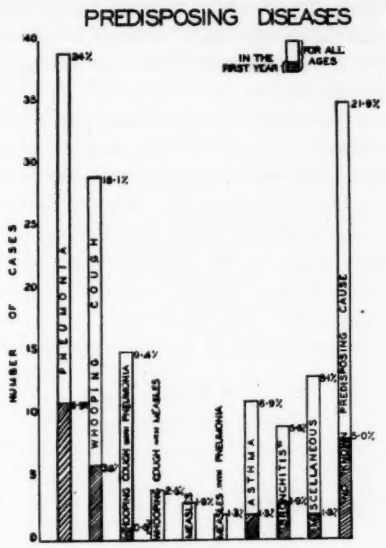

CHART 2

TABLES FOR CHART 2

PREDISPOSING DISEASES

Disease	Number of Cases	Percentage
Pneumonia	39	24.4
Pertussis	29	18.1
Pertussis with pneumonia	15	9.4
Pertussis and rubeola	4	2.5
Rubeola	3	1.9
Rubeola with pneumonia	2	1.3
Asthma	11	6.9
"Bronchitis"	9	5.6
Miscellaneous	13	8.1
No known predisposing cause	35	21.9
Total	160	100.0

PREDISPOSING DISEASES IN FIRST YEAR OF LIFE

Disease	Total	Percentage
Pneumonia	11	6.9
Pertussis	6	3.8
Pertussis with pneumonia	1	0.6
Asthma	2	1.3
Bronchitis	3	1.9
Polyp of larynx	1	0.6
Blue at birth	1	0.6
No predisposing cause	8	5.0

As seen in Table II, only 27 cases (16.9%) gave a history of less than one year's duration when first seen, but at the other end of the table there were 41 cases (25.6%) whose duration of illness was longer than 5 years before full investigation with bronchograms was done.

Thirty-nine (24.4%) of the 160 children had parents or grandparents with asthma but in only 15 of these did the child himself suffer from asthma (see p. 30). Thirty-one

children gave a family history of tuberculosis, but only 14 of these children had a positive Mantoux reaction (see page 30). One father suffered from bronchiectasis but the disease was only seen on two occasions in more than one sibling. Without control figures these facts are of doubtful significance.

Frequently children with bronchiectasis appear remarkably well, provided the disease is not too advanced or extensive. They grow and gain in weight and not uncommonly keep a good colour in their cheeks and mucous membranes. In fact, it is only the cough, runny nose, or recurrent colds, that appear to worry the parents, and in the dry summer months even these symptoms may practically disappear. The classical picture of bronchiectasis with cyanosis, dyspnoea, gross clubbing, foetid breath and quantities of foul-smelling sputum, is now fortunately comparatively rare in children; absenteeism at school is now a more useful criterion of the disability.

Dry bronchiectasis, where symptoms and physical signs were absent, occurred in only

TABLE II

DURATION OF SYMPTOMS

Years	Less than 1	1	2	3	4	5	6	7	8	9	Over 10	Indefinite more than 3	Indefinite	Total
Number of cases	27	24	18	17	12	11	16	5	4	3	2	13	8	160
Percentage	16.9	15.0	11.3	10.6	7.5	6.9	10.0	3.1	2.5	1.9	1.3	8.1	5.0	100.0

two cases, but subsequent follow-up shows that many cases become dry in early adolescence.

The symptoms recorded in Chart 3 were either noted in the history, or observed clinically, but were not always specifically asked for. Recurrent colds were frequent and in 12 cases (7.5%) the parents complained that the child appeared to be losing weight.

Sputum was usually expectorated after eight years of age. The younger child frequently has sputum, but tends to swallow it instead of coughing it up, and this is almost universally so under three years of age. Haemoptysis was rare, but was noted any time after three years. It was probably present before this age period, but, as already mentioned, the sputum was not seen. This is in contrast to the frequency recorded in adults. Bradshaw, Putney and Clerf[5] record a high incidence of haemorrhage (42 cases) in a series of 171 medically treated patients, but only 29 of the 171 were under 10 years of age and in the series presented here the symptom became more common as the child grew older.

Wheezing occurred in those cases suffering from asthma or as a concomitant symptom of bronchiectasis (see page 30). Dyspnoea, apart from asthma, was usually confined to the severe bronchiectatic.

Stridor only occurred where there was associated laryngeal disease.

The weight figures in Chart 4 demonstrate that a high percentage of children in this series were below average in weight. Although some of those grossly underweight were also suffering from asthma, these were in the minority, the detrimental factors being more particularly the extent of the disease and severity of the bronchiectasis, gross cystic bronchiectasis invariably being associated with a poor gain. While under observation,

113 cases (70.6%) showed a satisfactory gain in weight and 25 cases (15.6%) an unsatisfactory gain. The latter could usually be accounted for by the temporary arrest following operation. It was usual for most children, even those grossly underweight, to make a satisfactory gain while under observation in hospital, at convalescent homes, or even in their own homes while undergoing treatment. Some of them made excessive gains and this was not an uncommon occurrence after operation.

Chest deformity was tabulated under three categories: 1. The pigeon-breast. 2. De-

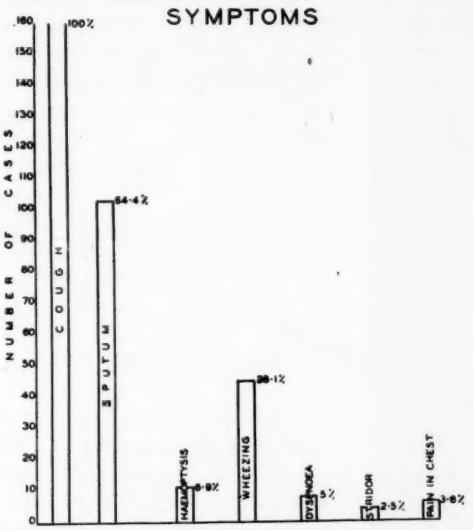

CHART 3

TABLE FOR CHART 3

SYMPTOMS. TOTAL NUMBER OF CASES—160

Symptom	Number of Cases	Percentage
Sputum	103	64.4
Haemoptysis	11	6.9
Wheezing	45	28.1
Dyspnoea	8	5.0
Stridor	4	2.5
Pain in chest	6	3.8
Loss of weight	12	7.5
Recurrent colds	18	11.3

pressions of ribs or sternum. 3. Barrel-shape. The pigeon and barrel chest need no description; there were 25 cases (15.6%) of the former and only 5 (3.1%) of the latter. But the deformities of depression were of all varieties, the commonest being a linear depression circumscribed around the lower third of the chest wall, known as Harrison's sulcus. Sometimes the lower end of the sternum was deeply depressed, or one side of the chest flattened. Often gross deformities had gone unnoticed by the parent, but in some cases the condition was observed to develop slowly after one of the lung-damaging diseases. In no case was the condition definitely noticed at birth. There were 40 (25%) cases in this group, but minor degrees of the deformity were unrecorded, so that this figure is probably a low estimate. The deformity developed more rapidly where the chest

wall was soft, as in young infants, or in children suffering from rickets, particularly in the first three years of life.

A large number of the children suffering from bronchiectasis were round shouldered, had protuberant abdomens and a lordosis. The repeated coughing with general loss of muscular tone probably accounts for this common deformity (Fig. 1). Scoliosis was rare in this series of cases, except as a temporary occurrence after lobectomy, or pneumonectomy. The majority of these deformities could be corrected with postural and breathing exercises if not too chronic, and even in those who had pneumonectomy the ultimate aim was a straight back and no flattening.

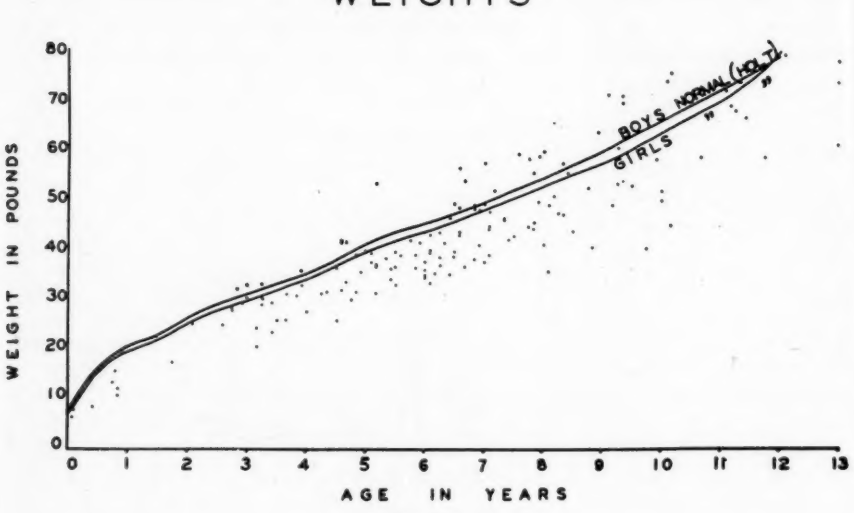

CHART 4

Physical signs in the chest were variable, not only from case to case, but from time to time in the same child. The signs seemed to vary according to the pathology in the surrounding lung, but when persistently confined to one area of the chest bronchiectasis was suspected. A change in percussion note compared with the normal side was not uncommon; usually the note was impaired, but sometimes it was hyperresonant if there was much compensatory emphysema. Alteration in the breath sounds from the normal vesicular type to either bronchial, tubular, or complete absence, was observed but commonly a poor air entry was all that could be detected.

Moist sounds were probably the most useful physical sign. If there was any secretion in the dilated bronchi, and this was invariably so except in the driest summer months, then on deep breathing rales were heard over the affected area, fine if the bronchioles were affected, or coarse if the larger bronchi were diseased. It was often necessary to make the child give a short cough, followed by a deep breath, before the moist sounds could be heard. If the signs were localized, they were of significance, but if generalized, they might be caused by an associated asthma or bronchitis, and only when the latter condition had subsided could the bronchiectatic areas be detected clinically. Friction sounds were rarely detected, although pleural involvement was sometimes seen at operation.

Clubbing was present in 78 cases (43.7%). Its presence did not appear to have any definite relation to the extent of the disease, but rather to the severity and virulence of the infection. It was observed to develop rapidly in cases showing an acute advancement of the toxic process, particularly those running a periodic fever. Usually, however, it took several months to a year or more to develop and was therefore not observed in any of the cases in the first year of life.

It usually cleared up after the diseased part had been removed at operation, taking a year or more to do so. In medically treated cases, considerable improvement in the degree of clubbing was observed with clinical improvement and in a few cases it disappeared in spite of bronchographic evidence of persistent bronchiectasis. Where the clinical condition deteriorated, clubbing sometimes developed or became more marked, but in no case was osteoarthropathy observed.

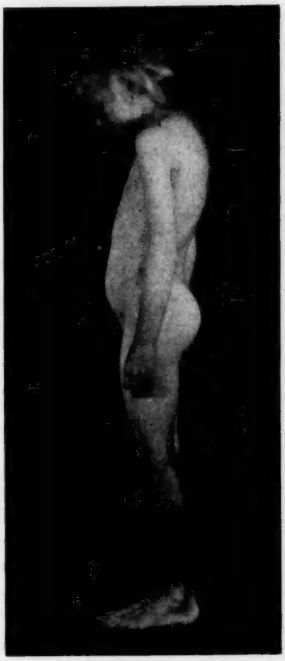

FIG. 1. Postural deformity commonly seen in chronic chest disease; round shoulders, lordosis and protuberant abdomen.

Cyanosis was comparatively rarely observed except in young infants with rapidly developing bronchiectasis, as from diffuse pneumonia, or in those cases associated with extensive disease or asthma. In this series, 14 cases (8.6%) showed cyanosis, and a number of those recovered their normal colour as the child's general condition improved.

Usually, bronchiectatic children do not have a raised body temperature unless they are suffering from an exacerbation, or flare up of the disease process. However, a few of the cases with extensive disease, or the gross cystic variety, used to run an irregular temperature up to 37.2° or 37.8° C., particularly in the evening.

The respiratory rate was usually normal unless there was an associated pneumonic flare up, or concomitant asthma. Those cases with extensive or advanced disease had a permanently raised respiratory rate of 25 to 35/min., but rarely exceeding this.

It is only possible in Part I to give a brief summary of the findings in regard to nasopharyngeal infection.

Clinical assessment of disease of the tonsils suggested that, owing to recurrent colds and sinus infection, and probably also from the coughing up of sputum, these children had larger and more infected tonsils and tonsillar lymph nodes than normal children.

Antral roentgenogram was done on 142 children and 108 (71.6%) of these had one or both antra opaque with 13 (9.1%) showing mucosal thickening. Of those showing positive roentgenographic findings, 100 cases were subjected to antral puncture and 80% showed muco-pus on one or both sides. This high incidence of sinus infection in bronchiectasis is the common finding, although the above figures are statistically inaccurate as the 18 children who did not have roentgenograms and the 21 children not subjected to antral puncture were those with minimal nasal symptoms. It does, however, demonstrate an important association between the two infections. Probably either condition predisposes to the other, but both infections can occur independently.

A diagnosis of asthma was made if the parent observed the child to have attacks of breathlessness, heavy breathing or wheezing, usually worse in the evening, or when in bed. The symptoms were asked for specifically and at least three or four attacks must have been recorded before the diagnosis was made. Not uncommonly, during an attack, numerous rhonchi with or without rales were heard diffusely over both lung fields. Fifty-three children (33.1%) suffered from these symptoms at one time or another. They were more common in the first seven years of life and thereafter the attacks grew less severe and less frequent and often completely disappeared. Some patients only suffered

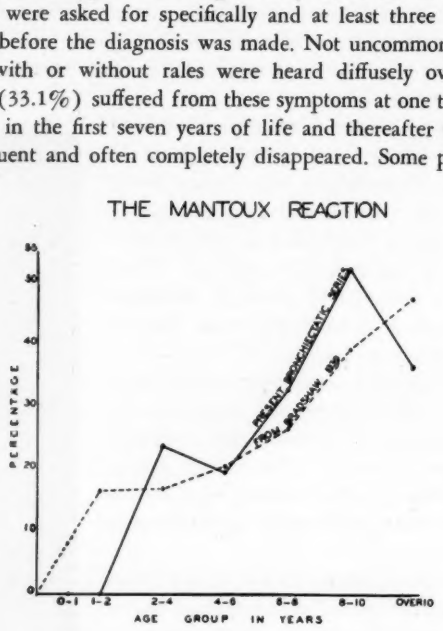

CHART 5

TABLE FOR CHART 5

MANTOUX REACTION

Age	0–2	2–4	4–6	6–8	8–10	Over 10	Total
Mantoux positive	0	5	6	17	13	4	43
Mantoux negative	7	16	25	35	12	7	104
Percentage positive in age group	0	23.8	19.4	32.7	52.0	36.4	29.2

from the condition for a year or two and then the symptoms subsided. The narrow lumen of a child's bronchial passages probably accounts for the frequency of asthmatic symptoms. Any slight swelling of the mucous membrane as may occur in chronically inflamed bronchi will narrow their calibre still further, so that a condition akin to obstructive emphysema is produced.

The Mantoux reaction (intradermal 0.1 cc. of 1 in 1,000 Old Tuberculin) was tested in 147 children. It was positive in 43 (29.2%) and negative in 104 (70.7%). Five of the negative reactions became positive while under observation. As would be expected, the incidence of positive reactors increased according to age (Chart 5).

Bradshaw[6] (1939) published the results of the intradermal tuberculin test, 1 in 1,000, in a series of children attending the outpatient department at the Hospital for Sick Children from 1934 to 1938. Of 3,010 cases tested, 748 (24.8%) gave a positive reaction (see Chart 5).

Although the numbers in this series are much smaller, the percentage Mantoux posi-

tive reactions is similar, therefore revealing no clear relationship between the Mantoux reaction and bronchiectasis.

In only four children was tuberculosis definitely diagnosed. Two of these had enlarged tuberculous glands pressing on a bronchus producing lobar collapse, in which bronchiectasis had developed; one had the rare condition of tuberculous laryngitis with a healed tuberculous lesion in the lingula and a collapse of the right middle lobe with bronchiectasis, the diagnosis being confirmed at autopsy. The fourth case was diagnosed at autopsy following removal of the right middle and lower lobes. In eight other cases with a strongly positive Mantoux reaction, a superadded tuberculous infection was suspected, but there was no real evidence to suggest that tuberculosis had produced the bronchiectasis except in those cases where an enlarged hilar gland had obstructed the bronchus.

The parent of each child in this series was questioned concerning the incidence of pneumonia at any time, and the results were compared with a series of 385 controls without chest disease collected from unselected children attending the outpatient department at Great Ormond Street. In the bronchiectatic series, 70% gave a history of this disease at one time or another as compared with 11% of the controls. This demonstrates the great importance of pneumonia either as a predisposing or complicating factor in bronchiectasis.

Only four children suffered from an associated congenital defect. These were a cleft palate, polypi of the larynx and vocal cords producing partial asphyxia, an abnormal artery discovered at operation, and stenosis of the trachea. The last two were associated with a cystic condition of the lung which in all probability was congenital in origin, otherwise there is little here to support a congenital theory of aetiology for most cases of bronchiectasis if we presuppose the multiplicity of congenital anomalies. The incidence of bronchiectasis is high in cases of situs inversus (Adams and Churchill[7]) although this anomaly was not present in this series.

The Diagnosis

It is expedient to discuss at this stage the diagnosis of bronchiectasis, as the importance of the study is at the clinical stage before a bronchogram is done. Although a roentgenogram without lipiodol may show various shadows suggestive of bronchiectasis, this can be most misleading, and therefore the diagnosis of bronchiectasis should at first be made clinically and then confirmed by bronchogram. Bronchoscopic examination, blood count, and sedimentation rate are unreliable adjuvants to the diagnosis and are therefore discussed later.

In this series no single symptom or sign was pathognomonic of bronchiectasis; it was a clinical syndrome that suggested the diagnosis, but since none of the features of this syndrome were constant, the summation of the findings and their individual importance had to be assessed before making the diagnosis. When in doubt, repeated observations made over a period of weeks often clarified the problem.

A constant cough, present day and night over a period of several months, was an important symptom, particularly if it followed pneumonia or pertussis. The periodicity of associated asthma tended to detract attention from the constant underlying cough unless this was specifically asked for.

Mucopurulent sputum, when coughed up, was a helpful sign in the diagnosis, particularly if most profuse on rising in the morning, as secretions collect in the dilated

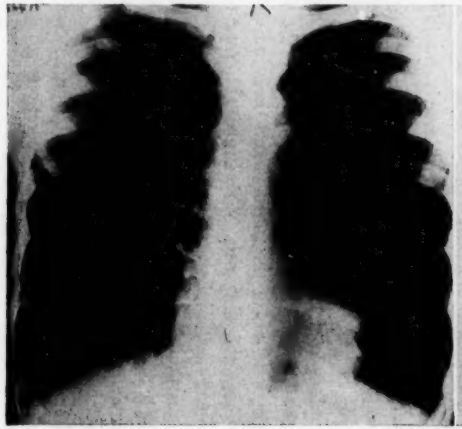

FIG. 2. Roentgenogram showing increased hilar and linear basal markings commonly seen in bronchiectasis.

FIG. 3. Right lateral roentgenogram. Note hypertranslucence in lower lobe area, site of bronchiectasis in Fig. 4.

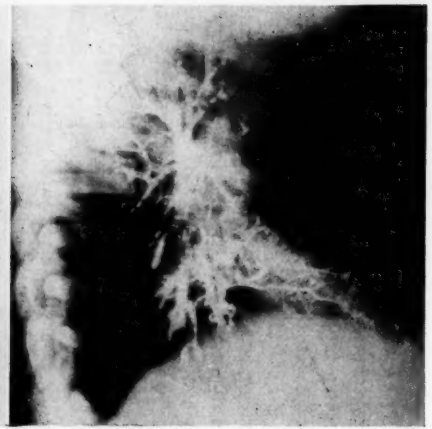

Fig. 4. Right lateral bronchogram from same case (Fig. 3.) Bronchiectasis in right lower lobe and proximal part of right middle lobe. Note unusually long distal branches of normal calibre in right middle lobe.

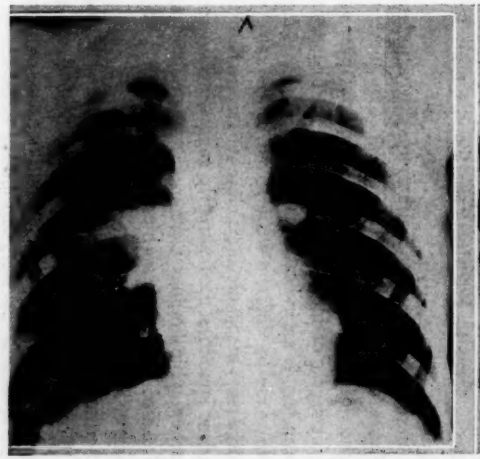

FIG. 5. A. P. roentgenogram showing collapse of pectorai segment of right upper lobe simulating hilar flare in A. P.

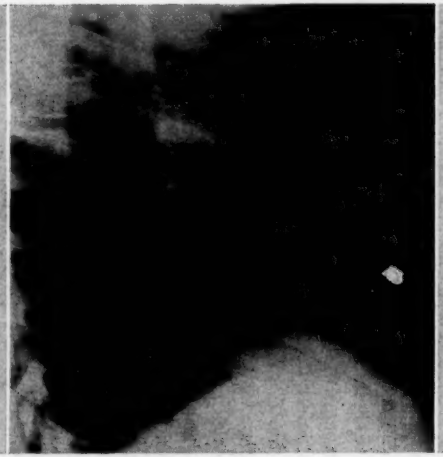

FIG. 6A. Right lateral roentgenogram; same as Fig. 5.

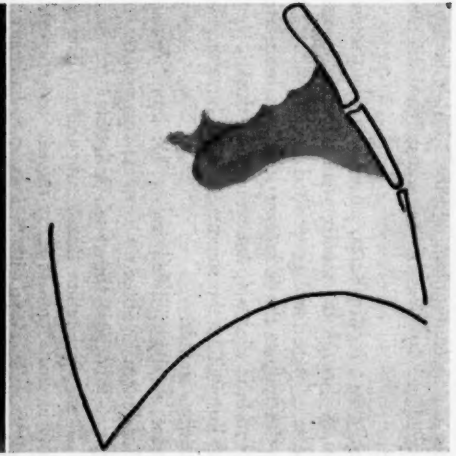

Fig. 6B. Line drawing of Fig. 6A.

bronchi overnight. The white mucoid sputum in asthma had to be differentiated, but the mucopurulent sputum produced by sinusitis was indistinguishable from bronchiectatic sputum.

Rales, constantly heard over a localised area, particularly when accentuated by a cough followed by a deep breath through the mouth, were important signs. In diffuse bronchiectasis, however, the rales were more generalised and in such cases weekly clinical examinations helped to differentiate the inconstant sounds in bronchitis or asthma from the more persistent rales of bronchiectasis; sometimes the asthmatic signs failed to resolve until after admission to hospital. In the summer months, however, some bronchiectatic children had no adventitious sounds.

Clubbing when present usually signified irreversible bronchiectasis providing there was no congenital cardiac lesion. Its absence was of no significance.

In asthma and recurrent bronchitis the cough is intermittent in character, and the sputum a whitish mucoid material rather than mucopurulent. The adventitious sounds are inconstant and diffuse in character with many rhonchi and emphysema is common.

Pertussis produces a spasmodic cough with periods up to half an hour without coughing. The child goes red in the face with coughing, frequently vomits and has difficulty in getting his breath after the coughing bout. The sputum is scanty and mucoid. In uncomplicated pertussis the absence of physical signs in the chest in association with a really distressing cough always suggests the diagnosis.

With nasopharyngeal infection, the cough is constant or intermittent in character, often being described as a "throat" cough. If there is associated sinus infection, mucopurulent sputum is frequently expectorated, but abnormal physical signs in the chest are absent unless there is an associated bronchitis. One good cough, however, will clear the adventitious sounds, so distinguishing the condition from bronchiectasis where the rales are accentuated on coughing.

Cough is an insignificant symptom in tuberculosis on the whole, lassitude, loss of weight and general malaise being the usual complaints. The absence of sputum and clubbing and adventitious sounds in the chest help to distinguish the condition from bronchiectasis, except in the rare adult type occasionally seen in the older child. Sometimes a large tuberculous hilar gland pressing on a bronchus produces a "brassy" cough, or even lobar collapse predisposing to bronchiectasis, the diagnosis being confirmed by bronchoscopy.

Lobar collapse and unresolved pneumonia are frequently associated with bronchial dilatation, so that in these conditions the chief problem is to know whether the dilatation is reversible. Duration of illness combined with bronchographic evidence that dilatation has been present for a year or more, particularly if the dilatation is greater toward the periphery of the bronchus, is an indication suggesting that it is irreversible.

No attempt has been made to differentiate infected congenital cystic disease of the lung and cystic bronchiectasis. There were some clear cut cases where symptoms of cough and profuse mucopurulent sputum started abruptly suggesting sudden infection of the cysts, and certain bronchographic findings were in favour of the diagnosis, but in this series all have been classified as cystic bronchiectasis. Before cysts become infected they give rise to few symptoms or signs unless of large size.

Characteristically, in pancreatic fibrosis, the cough is dry and bronchial secretions are tenacious and difficult to cough up. Not uncommonly moist sounds are absent in the chest, but roentgenogram usually shows increased hilar and lung markings with emphysema not unlike the findings seen in asthma; in fact, superadded asthmatic symptoms sometimes

occur. Some disturbance of bowel function associated with poor gain in weight from birth suggests the diagnosis which is confirmed by the absence of pancreatic trypsin in the duodenal juice. Pathogenesis of the lung condition remains obscure but it does not appear to start as bronchiectasis although it may progress to this later.

It was seldom possible to make a definite diagnosis of bronchiectasis by roentgenogram without bronchography. In conjunction with the history and clinical signs, the diagnosis was suggestive when linear markings (Fig. 2) or an opacity were seen in the roentgenogram. Less frequently mottled opacities were seen and in five cases definite cystic areas were seen. Usually the markings were fairly dense and coincided with the diseased area but occasionally this was deceptive where surrounding emphysema obscured the linear markings (Figs. 3 and 4) or where the heart shadow prevented the detection of left lower lobe disease. Upper lobe markings were rarely noted because compensatory emphysema commonly occurs at the apices. Furthermore, the most frequently involved segment—the pectoral—gives more the appearance of a hilar flare than an upper lobe lesion in an antero-posterior view (Figs. 5 and 6a and b). Generalized emphysema occurred in association with asthma or diffuse bronchiectasis in 10 cases but compensatory emphysema was not a common finding in association with collapse.

Bronchography is the only available method for accurate diagnosis of bronchiectasis in life and is a necessary investigation to determine the type and extent of the lesion and its suitability for surgical treatment. If the bronchial dilatation was greater toward the periphery than near the stem bronchus (club-shaped), it was considered a permanent condition and irreversible, and therefore suitable for surgical removal. But where the dilated bronchus was of equal diameter along its length, reversion to normal calibre was considered possible and the child referred for repeat bronchograms in a year or two. It has been necessary in some children to repeat the bronchograms several times over a period of years before the picture clarifies itself into reversible or irreversible bronchiectasis. But even with a series of bronchograms obtained in this way over several years, the possibility of transient changes in the intervals increases the difficulty of diagnosing permanent dilatation (Part III, to be published).

The technic of bronchography in children has been fully described by Moncrieff, Pilcher and Field.[8] The method was followed in detail except for some of the older children when local novocaine anaesthesia for insertion of the special intratracheal needle was adequate instead of the usual gas-oxygen anaesthesia. For children under five years, the nasal method under open ether anaesthesia was used. It has been the practice recently to do the right bronchogram first ensuring a clear right lateral roentgenogram; then, if the child's condition is satisfactory, to proceed straight away with the left bronchogram taking a left oblique roentgenogram.

For simplification, the varieties of bronchiectasis demonstrated by bronchography have been divided into four types.

Chart 6 shows the relative frequency of the various types of bronchiectasis and Figs. 7 to 10 show an example of each type. The varicose type, which has been described by Kerley,[9] is a diffuse, irregular dilatation often referred to as moniliform (Fig. 10), and in some cases it appears as if the soft parts of the bronchial wall have dilated, but the cartilage rings remain intact. Varicose bronchiectasis often produces only slight symptoms and signs. The indefinite group was difficult to classify. Five of these were infants in the first year of life, diagnosed at autopsy.

It is difficult to say what factors determine the type of dilatation that will develop. The varieties were classified according to the age of the child, but no significant differ-

ence was detected. The impression gained was that the cystic variety was either congenital in origin, or followed a virulent infection of the lungs, producing rapid destruction of the bronchial wall, particularly in the smaller bronchi and bronchioles. The tubular variety was frequently associated with lobar collapse, but also not uncommonly seen with asthma, producing a mild diffuse type. The fusiform variety was rare (Part III, Fig. 5, to be published), but was observed in a brother and sister in one family. The varicose type was more common in the older age groups, seven cases dating the age of onset of symptoms at five years. However, five of these cases could not relate the onset to any particular illness or infection, so it is suggested that this type of bronchiectasis tends to result from a less virulent infection in an older child with more resistance to the damage of the bronchial wall.

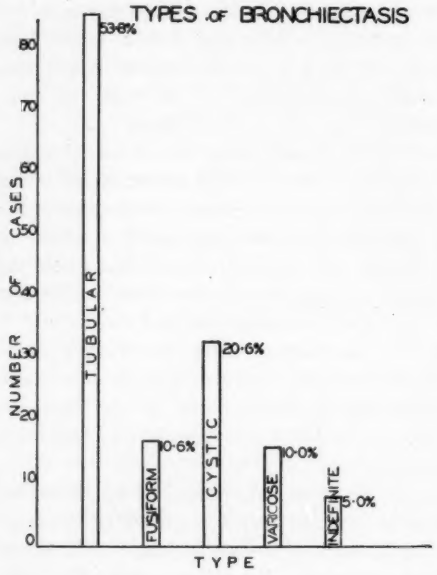

CHART 6

TABLE FOR CHART 6

TYPES OF BRONCHIECTASIS

Type	Number of Cases	Percentage
Tubular*	86	53.8
Fusiform	17	10.6
Cystic	33	20.6
Varicose	16	10.0
Indefinite	8	5.0
Total	160	100

* Club ends were frequently observed in this type.

The site of the bronchiectasis was determined according to the bronchi that were seen dilated in the bronchogram, or according to findings at operation and autopsy.

Chart 7 demonstrates the preponderance of disease on the left side and this is confirmed in Table III, where the combination of left lower and lingula lobes was the commonest lesion, yet in no case was the lingula affected alone.* As Lander and Davidson[10] have pointed out, following collapse of the left lower lobe, the direction of the upper lobe bronchus is altered. Usually the lingula bronchus was displaced downwards medially and backwards, thus producing a sharp bend at its origin making drainage of secretions difficult. Observations on the right side showed a similar train of events following collapse of the right lower lobe. This affected drainage of the right middle lobe and indirectly affected the pectoral (antero-lateral) branch of the right upper lobe, which

* Isolated lingula disease has been noted since these records were completed.

TYPES OF BRONCHIECTASIS SEEN

FIG. 7. Left oblique bronchogram showing tubular bronchiectasis of left lower and lingula lobes.

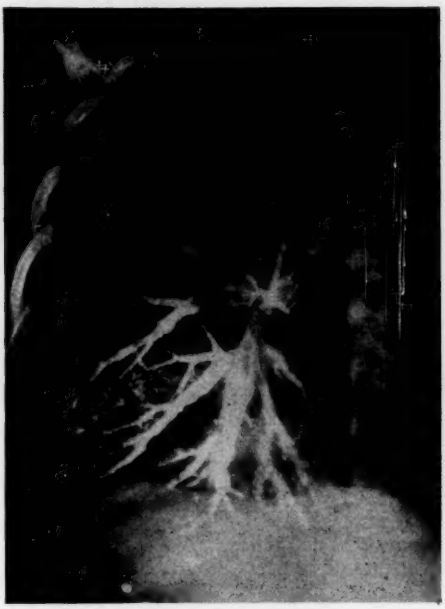

FIG. 8. Left oblique bronchogram showing generalized fusiform bronchiectasis.

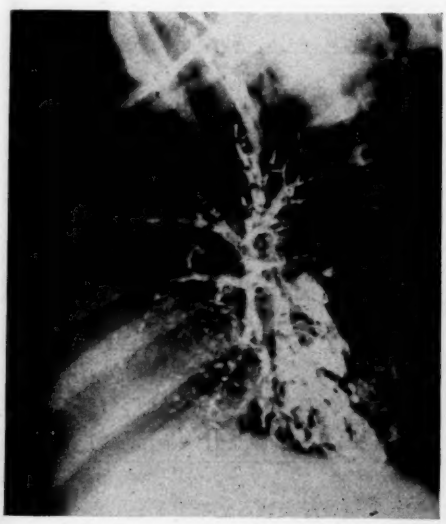

FIG. 9. Left oblique bronchogram showing cystic bronchiectasis of left lower lobe with crowding of bronchi suggesting collapse, caused by tuberculous hilar gland compressing bronchus.

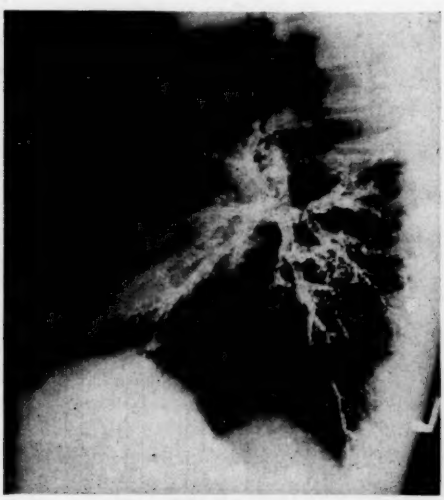

FIG. 10. Left oblique bronchogram showing generalized varicose bronchiectasis.

TABLE III

COMBINATION OF LOBES AFFECTED IN EACH CASE

Site (Lobe)	Number of Cases	Percentage
Lingula and left lower	22	13.8
Diffuse both lungs	20	12.5
Right middle and right lower Left lower and lingula	20	12.5
Left lower	16	10.0
Whole right lung Left lower and lingula	9	5.6
Right middle and right lower	8	5.0
Right middle and right lower Left lower	7	4.4
Right middle	7	4.4
Right middle Left lower and lingula	7	4.4
Whole right lung	6	3.8
Right lower Left lower	5	3.1
Right middle Whole left lung	5	3.1
Whole left lung	3	1.9
Whole right lung Left lower	3	1.9
Right lower Lingula and left lower	3	1.9
Other combinations	19	11.9
Total	160	100

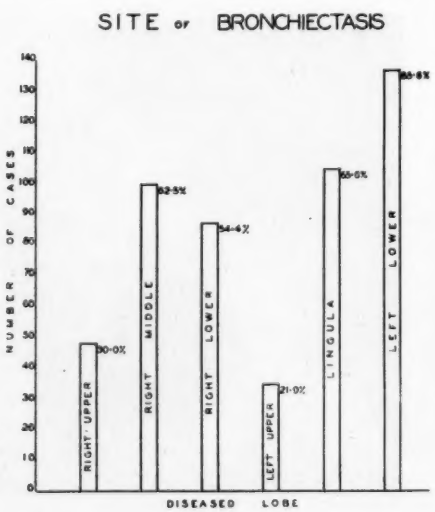

CHART 7

TABLE FOR CHART 7

NUMBER OF CASES IN WHICH LOBES WERE AFFECTED

Site (Lobe)	Number of Cases	Percentage
Right upper	48	30.0
Right middle	100	62.5
Right lower	87	54.4
Left upper	35	21.9
Lingula	105	65.6
Left lower	137	85.6
Number of cases investigated	160	

was displaced medially and downwards, so that the bronchus made a sharp bend with the main bronchus, thus creating difficulties in drainage. This combination of pectoral branch of right upper lobe, right middle lobe and right lower lobe was not at all uncommon, as will be seen in Table III, where it is described as "whole right lung" because the three lobes are affected.

The reason for the great preponderance of lower lobe disease is best explained by gravity impeding drainage of secretions, the longer, more curved, left main bronchus probably accounting for the higher percentage in the left lower lobe. But in only one case was the right lower lobe affected alone, yet in 5% of cases it was affected with the middle lobe. The other significant feature of Table III is the high incidence (4.4%) of the right middle lobe disease only. In an attempt to explain this, it is worth mentioning an anatomic peculiarity of the right middle lobe bronchus, as described by Brock.[11] The bronchus arises from the main stem at an acute angle, passes downward in close proximity to the right lower lobe bronchus for a short distance, then bends forward in a curve. This probably causes difficulty in drainage of secretions, particularly following collapse of the lobe, when accentuation of this curve has often been noted.

TABLE IV

INCIDENCE AND LOBAR DISTRIBUTION OF MASSIVE COLLAPSE IN 160 CASES OF BRONCHIECTASIS

Site of Collapse	Number of Cases	Percentage of Total 160 Cases
Right upper lobe	10	6.3
Right middle lobe	35	21.9
Right lower lobe	19	11.6
Left upper lobe	7	4.4
Lingula lobe	15	9.4
Left lower lobe	42	26.3

N.B. Pulmonary collapse can occur in more than one lobe in the same child so that the total figure is greater than 74.

Why then should the upper lobes and dorsal branch of the lower lobe enjoy comparative freedom from bronchiectasis? These are the lobes whose bronchi run horizontal or downwards to the main bronchus so that gravity assists drainage and at the same time there are no anatomic peculiarities to impede drainage.

Summarising the facts arising from the study of the site of the affected areas, the disease had a predilection for lobes whose bronchi were directed upwards against gravity towards the main bronchus and those which had an atomic peculiarity impeding drainage. Both these conditions prevented proper drainage of secretions, a fact which supports the theory that inadequate drainage of secretions is one of the predisposing causes of bronchiectasis.

It is not always easy to differentiate between consolidation and lobar collapse in a roentgenogram, and frequently the two conditions are present in association. However, in an attempt to assess the incidence of massive pulmonary collapse in association with bronchiectasis, all cases showing homogeneous opacities in the roentgenogram characteristic of lobar collapse were recorded. Three criteria for the diagnosis of collapse were made: 1. The opacity, being the whole or part of a lobe, occupied a smaller area than

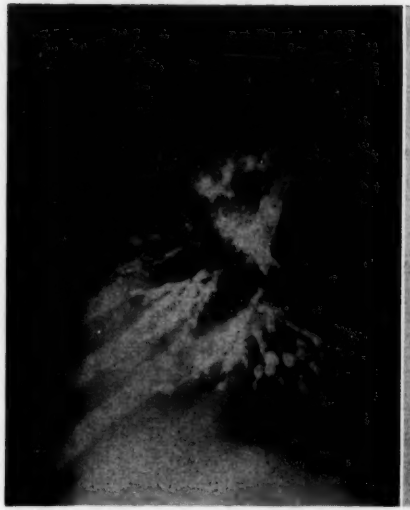

FIG. 11. Left oblique bronchogram showing almost cystic dilatation of left lower and lingual bronchi. Note consolidation rather than collapse of this area.

FIG. 12. Left oblique bronchogram of same case (Fig. 11) taken 3 mos. later. Bronchi have reverted to normal calibre.

FIG. 13. Left oblique bronchogram showing crowding and dilatation of bronchi in collapsed left lower lobe.

FIG. 14. Left oblique bronchogram of same case (Fig. 13) 10 mos. later. Bronchi have returned to normal calibre.

FIG. 15. Right lateral brochogram of girl aged 8 2/12 yrs., showing crowding and almost cystic dilatation of right middle and lower lobe bronchi.

FIG. 16. Right lateral bronchogram of same case (Fig. 15) taken 2 yrs. later. There is re-expansion of right middle and lower lobes but some permanent bronchiectatic changes persist.

the normal lobe, or part of a lobe, was expected to occupy. 2. One of the margins was concave. 3. In the bronchogram, the bronchi showed crowding.

The total number of cases showing one or more areas of massive collapse was 74 (46.3%), and, as shown in Table IV, the left lower lobe and right middle lobe were most commonly involved. This does not mean to say that alveolar collapse was not present in the remaining 53.7% of cases, but merely that if collapse was present, it was not sufficient to produce the characteristic opacity in the roentgenogram. The figures for the upper lobes are deceptive, as all except one case were associated with massive or diffuse collapse of the whole lung, which means that isolated collapse of an upper lobe was rare. In 12 cases, the massive collapse re-expanded when examined by roentgenogram but bronchial dilatation persisted. In two cases, the re-expanded lobe collapsed again and persisted in a collapsed state.

It is well known that bronchi will dilate in the presence of collapse. In a normal subject on inspiration, all structures inside the chest are subjected to a negative pressure. Free entry of air into the alveoli prevents the negative pressure from becoming excessive, but where the passage of air into some alveoli is blocked the negative pressure increases (Habliston[12]) and acts directly on the bronchus supplying the obstructed alveoli and dilatation occurs. As long as there is a possibility for the alveoli to re-expand, the dilatation must be considered reversible providing the damage to the bronchial wall by infection has not been too severe. But there appears to be a time limit for this re-expansion. It must frequently happen that some alveoli open up again while others remain obstructed, and this probably allows for readjustment of pressures and gradual improvement of the bronchial dilatation as has been observed in many cases over the years (Figs. 15 and 16). During these studies into chronic chest disease in childhood, this reversibility of bronchial dilatation has been frequently observed.

In only two cases could the duration of the bronchial dilatation be assessed with any degree of accuracy. Fig. 11 shows the bronchogram of a girl aged 5⅓ years who had had cough and dyspnoea since an attack of tonsillitis 2½ months previously. There was almost cystic dilatation in the left lower and lingula lobes in association with what appeared to be consolidation and not collapse. One month later the condition had cleared and Fig. 12 shows that the bronchi had reverted to normal calibre. This case is of particular interest in so much as it shows that consolidation as well as collapse can produce dilatation of the bronchi. Figs. 13 and 14 show the bronchograms from a girl aged 6 years, 5 months, with collapse of the left lower lobe of six months' duration.

The collapsed lobe may show radiologic evidence of expansion but some bronchial dilatation may persist. Figs. 15 and 16 demonstrate this phenomenon. As previously stated, this probably signifies incomplete expansion with permanent bronchiectatic changes. Intermittent collapse in bronchiectatic areas probably accounts for the fluctuation in dilatation of the bronchi not infrequently seen in repeat bronchograms.

Bronchoscopy in children as an aid to diagnosis of bronchiectasis is of doubtful value. Of the present series of 160 cases of bronchiectasis, 99 were subjected to bronchoscopy. The abnormal findings seen included red or oedematous mucous membranes with or without excess mucus or muco-pus. Although there was a tendency for these changes to be found predominantly in bronchi that were diseased, nevertheless, it was not uncommon to find them in other bronchi that showed no bronchiectasis in the bronchogram, so that the bronchoscopic findings would have been misleading as a means of diagnosing the site of the bronchiectasis. There are many pathologic conditions other than bronchiectasis

that will give similar bronchoscopic findings, and it is a fallacy to imagine that minor degrees of dilatation of the bronchi can be detected by this means. Furthermore, in 5 of the 99 cases of bronchiectasis the bronchi appeared normal at bronchoscopy, although they were seen to be diseased in the bronchogram.

There was no planned investigation into the effect of bronchiectasis on the erythrocyte sedimentation rate or on the blood count. These investigations were performed sporadically for various reasons while the patient was in the hospital. However, after excluding as far as possible the effect of coincidental infections or of special treatment, the following conclusions were made.

One hundred sixty-three determinations of erythrocyte sedimentation rate were done on 88 patients in the series of 160 bronchiectatic children. The majority of readings ranged between 10 and 25 mm., the maximum being 68 mm. (Micro-Westergren technic, normal 2-10 mm./hr.). It was no help in diagnosis, as some cases with extensive disease gave

TABLE V

COMPLICATIONS

Complication	Number of Cases	Percentage
Pneumonia	26	16.3
Otitis media	11	6.9
Nephritis	6	3.8
Empyema	2	1.3
Abscess of lung	1	0.6
Gastroenteritis	1	0.6
Vulvovaginitis	1	0.6
Pyelitis	1	0.6
Giant urticaria	1	0.6
Total	50	31.3

normal readings. There was a tendency for it to rise in association with inflammatory exacerbation in the lungs and for it to fall following rest in bed, but it was of no prognostic value and a raised reading was not a contra-indication to ambulant treatment. In fact, the sedimentation rate was not found helpful.

Of 85 children investigated, only six showed any significant degree of anaemia. It was concluded, in this series of bronchiectatic cases, that little effect of the disease was reflected in the haemoglobin, erythrocyte count or leucocyte count. In a few cases showing an exacerbation of symptoms in the chest, or a severely toxic condition, the commonest findings were reduction of haemoglobin and red cell count with normal colour index, a polymorphonuclear leucocytosis and a rise in sedimentation rate. As these findings are variable and inconsistent, they are of little value in assessing the progress of the disease, particularly as they are subject to alteration by so many other factors, including intercurrent infection, drugs and operations.

There have been surprisingly few complications so far during the period of observation up to 10 years (see Table V). If immediate postoperative conditions are excluded, 26 (16.3%) cases developed pneumonia, in 5 (3.1%) cases it was recurrent, and in 7 (4.4%) cases it was a contributory cause of death. There appeared to be little difference in susceptibility to pneumonia in pre- and postoperative patients, but the follow-up

is as yet far too short a period to give any figures of statistical value, or a definite opinion. Empyema only occurred in two cases, both fulminating cases. In one of these cases there was also an abscess in the left lower lobe.

Excluding the infectious fevers, probably the commonest intercurrent infection was in the nose and throat, a streptococcal sore throat being particularly common. This probably gave rise to the other two complications of any frequency, otitis media and nephritis. Eleven (6.9%) cases suffered from otitis media and two of these required mastoidectomy. There were 6 (3.8%) cases of acute nephritis. How far the streptococcal infection is the result of cross infection during frequent stay in hospital is difficult to assess. Only one case developed nephritis after an operation on the nose and throat; the remainder occurred spontaneously, but all while the child was an inpatient. The other complications were probably coincidental having no connection with the bronchiectasis.

Conclusions

In a study of 160 cases of irreversible bronchiectasis in childhood the following observations have been made:

From the history given by the parents, it was found that the age at onset of symptoms lay in the first year of life in approximately one fifth of the cases, the number thereafter declining with advancing age (except for a slight and possibly insignificant rise at age 5). In 55.6% of cases the parental history associated the onset of symptoms with an attack of pneumonia or pertussis.

The characteristic features of the disease included a constant cough with or without sputum (this is often swallowed by children). Haemoptysis was rare, but in 33.1% of cases there were associated asthmatic symptoms. More children were underweight than overweight for age and many had abnormal chest deformities. Clubbing occurred in 43.7% and when present was diagnostic of irreversible bronchiectasis in this series. Physical signs in the chest were variable, but the most useful diagnostic finding was localized rales on deep inspiration over the suspected area of lung.

In comparison with nonpulmonary and normal children, there was a marked increased incidence of pneumonia at all ages. There was, however, no suggestion that bronchiectasis increased or decreased susceptibility to tuberculosis.

Sinusitis is frequently associated with bronchiectasis although its exact relationship remains obscure.

In diagnosis, roentgenographic findings are frequently inconclusive, unless confirmed by bronchogram. Bronchography is by far the most important diagnostic procedure and is an invaluable method of studying the development of the disease.

Tubular dilatation was the commonest type of bronchiectasis.

In 85.6% of cases the disease was situated in the left lower lobe, and in 65.6%, in the lingula lobe, but in no case was the lingula affected as the only lobe. The disease has shown a predilection for lobes whose bronchi are directed upwards against gravity towards the main bronchus and those which have an anatomic peculiarity impeding drainage.

Massive collapse of the lung was associated with bronchiectasis in 74 (46.3%) cases.

It is important to recognize in children that bronchial dilatation may be reversible. In the diagnosis of irreversibility, duration of the dilatation and its contour are helpful.

Bronchoscopy was not helpful in diagnosis or localization of bronchiectasis.

The sedimentation rate was frequently raised, but was of little help in assessing activity

of the disease. Alterations in the blood count were few and usually only of significance in severe active cases of the disease.

Complications were infrequent, the commonest being pneumonia which occurred in 16.3% of cases.

ACKNOWLEDGMENT

These studies have been carried on by the medical and nursing staff and almoners of the Hospital for Sick Children, Great Ormond Street, the University College Hospital and the base hospitals at Hemel Hempstead and Stanboroughs, England. Acknowledgment is made to Drs. W. G. Wyllie and W. J. Pearson and Prof. R. S. Pilcher for continued advice and support and permission to study and record their cases, and to Mr. James Crooks for much of the nasopharyngeal and bronchoscopic treatment.

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SPANISH ABSTRACT

Bronquiectasia en el Niño 1. Estudio Clínico de 160 Casos

Se hicieron las siguientes observaciones en un estudio de 160 cases de bronquiectasia en la niñez:

De los datos proporcionados por los padres se encontró que la edad para al comienzo de los síntomas es en el primer año de vida en aproximadamente una quinta parte de los casos, el número por consiguiente baja con el aumento en la edad (excepto por un posible, ligero e insignificante aumento a la edad de cinco años).

En 55.6% de casos los datos de los padres asociaciaron el principio de los síntomas con un ataque de neumonía o pertussis.

Las características de la enfermedad incluyen una tos constants, con o sin esputo (éste se lo tragan muy amenudo los niños). La hemóptisis fué rara, pero en 33.1% de los casos se encontraron asociados síntomas asmáticos. Habían más niños que pesaban menos que más para su edad y muchos tenían deformaciones de pecho anormal. Las señas físicas en el pecho eran variables; pero el descu-

brimiento diagnóstico más útil fueron los estertores localizados en la inspiración profunda sobre area del pulmón sospechada.

En comparación con niños normales y no pulmonares, hubo una incidencia aumentada y marcada de neumonía a todas las edades. No hubo, sin embargo, ninguna sugerencia de que la bronquiectasia aumentaba o disminuía la susceptibilidad a la tuberculosis.

En la diagnosis los descubrimientos roentgenográficos son frecuentemente inconclusivos, al menos que sean confirmados por un broncograma. La bronchografía es el procedimiento diagnóstico más importante y es un método de much o valor para estudiar el desarrollo de la enfermedad.

La dilatación tubular era el tipo más común de bronquiectasia.

En 85.6% de los casos la enfermedad estaba situada en el lóbulo inferior izquierdo, y en 65.6% en el lóbulo língula, pero en ningún caso fué la língula afectada como el único lóbulo. La enfermedad ha mostrado una predilección por lóbulos, cuyos bronquios están dirigidos hacia arriba contra la gravedad hacia el bronquio principal y aquellos que tienen una peculiaridad anatómica que impide el drenaje.

El colapso macizo del pulmón fué asociado con bronquiectasia en 74 (46.3%) de los casos.

Es importante reconocer en los niños que la dilatación bronquial puede ser reversible. En la diagnosis de irreversibilidad, la duración de la dilatación y su contorno ayudan mucho.

La broncoscopía no fué útil en la diagnosis o localización de la bronquiectasia.

El tipo de sedimentación fué frecuentemente su ido; pero fué de poca ayuda en calcular la actividad de la enfermendad. Las alteraciones en el cuento globular fueron pocas y generalmente sólo de significancia en casos activos serveros de la enfermedad.

Las complicaciones no fueron frecuentes, siendo la neumonía la más común, la que ocurrió en 16.3% de los casos.

Great Ormond Street

PORPHYRINURIA

Report of an Unusual Case

By NORMAN C. WOODY, M.D.
Corpus Christi, Texas

ABNORMALITIES of porphyrin synthesis are of particular interest due to the bizarre nature of resulting manifestations. In the present clinical situation these asserted themselves in a fashion not hitherto reported.

The literature dealing with porphyrins and porphyria is enormous. Several clinical classifications have been proposed, the most recent listing two types: (1) the congenital or light-sensitive form; (2) the intermittent acute acquired form.[1] In the former there is familial occurrence, appearance of symptoms in childhood, photosensitization of the skin with resultant blistering, necrosis and scarring, occasional reddish discoloration of the urine and teeth, and subsidence of most symptoms in adolescence. Type I isomers of uroporphyrin and coproporphyrin are present in large amounts in the urine.

The intermittent acute type probably is also inherited but usually appears first in adults who rarely exhibit sensitivity to light. It is a chronic disease manifested by acute episodes of abdominal cramps, neurogenic paralysis, mental symptoms and dark urine. Waldenström[2] and others[3,4] have stated that large amounts of "type III uroporphyrin" are excreted in the urine of patients with the intermittent acute form. More recently, Watson et al.[5,6] have shown that the Waldenström "type III uroporphyrin" is largely uroporphyrin I (melting point of the methyl ester 284° C.) with an admixture of a previously undescribed porphyrin whose methyl ester melts at 208° C. It thus appears that classifications which link the congenital form of porphyria to excessive excretion of uroporphyrin I and the intermittent acute form to increased excretion of "uroporphyrin III" are more neat than accurate.

As a means of identifying the "uroporhyrin III" complex, Watson and associates employ the term "Waldenström uro-type porphyrin" and their nomenclature will be followed in this description.

The idiopathic forms usually are familial.[1-4] Toxic forms may be indistinguishable clinically, but differentiated by identification of a precipitating factor—lead sulfanilamide, sulfanol, trional, veronal, acetanilid or nitrobenzol[2,3,7]—and are best termed secondary coproporphyrinuria.[1] Nesbitt used the term *porphyria* to denote a marked increase of uroporphyrin or coproporphyrin excretion as the result of an inborn error of metabolism, and *porphyrinuria* to designate a similar increase caused by recognizable precipitating factors.[4]

The following patient does not fit into previous classifications but represents what might be called *passive porphyrinuria.*

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(Received for publication Sept. 20, 1948.)

CASE REPORT

E. T., a premature Negro girl, was born in Charity Hospital.

*Maternal History.**—The mother, a 37 yr. old Negro, had rather classic symptoms and signs of acute idiopathic porphyria for 2½ yrs. prior to the birth of this infant. Shortly before delivery, clinical and laboratory studies showed marked hepatic dysfunction, anemia which did not respond to treatment, hypertension and pyelonephritis. During the last month of pregnancy, oral alimentation became so poor that daily supplemental parenteral feedings were necessary. For these reasons pregnancy was terminated after an estimated gestation of 9 lunar mos.

At the time of delivery, excessive amounts of the Waldenström uro-type porphyrin were being excreted in the urine.

Birth Record.—Delivery was accomplished by cesarean section. No premedication was given and for anesthesia only local procaine was employed. Amniotic fluid and the vernix were not abnormally stained. Placenta was grossly normal though subsequent microscopic examination showed small infarcted areas. The infant weighed .9 kg. and was in poor condition. She responded well to resuscitative measures and was sent to the Premature Station. The mother died 8 days after delivery.

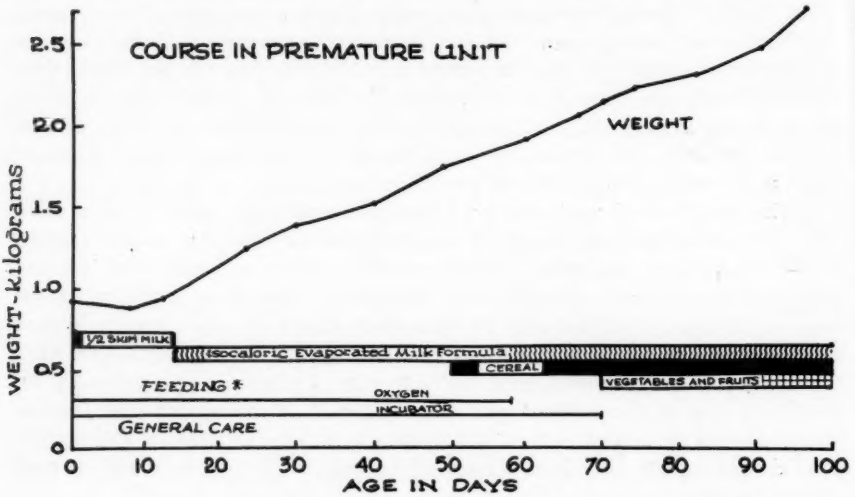

CHART I

Subsequent Course.—When examined in the Premature Station, the infant demonstrated no congenital abnormality, birth injury, icterus or enlarged organs. An abundance of blood-tinged mucus in the nose and mouth gave some difficulty for the first 24 hrs. Thereafter, the airway remained clear. Body temperature was stabilized in the incubator by the 8th day.

Because of known maternal infection and suspected but unproved terminal bacteremia, the infant received penicillin 5,000 units intramuscularly every 3 hrs. for 6 days. Other measures were those routinely employed in the hospital for premature infants—incubator care with adjustable temperature, relative humidity, and increased oxygen concentrations until the initial period of instability had passed, feeding with isocaloric formulae low in fat content, added vitamin and mineral supplements, and constant care. The infant's hospital course is summarized in Chart I.

She was discharged at the age of 96 days weighing 2.7 kg. The only physical abnormality was a

* The author is indebted to Dr. W. G. Unglaub of the Department of Medicine for details of the maternal illness. A complete description of the maternal findings will appear in a publication now in preparation.

small umbilical hernia which has since disappeared. The most striking feature, then, as now, was the contrast between her developmental attainments and her body mass. She has developed in orderly fashion in relation to her chronologic age, holding her head erect at 3 mos., sitting at 8 mos., and pulling herself erect at 11 mos. Untinted teeth appeared at 7 mos. At 11 mos. her skeletal age is

FIG. 1. Infant at age 11 mos.

normal (2 carpal centers). She is well nourished and well proportioned, but still small enough to cause suspicion of true primordial dwarfism: she weighs 6.2 kg. and her crown-heel length is 64.8 cm. (see Fig. 1).

TABLE I

URINARY EXCRETION OF PORPHYRINS*

	Color	Coproporphyrin			Waldenström Uro-type Porphyrin (μg.%)	Porpho-bilinogen
		Total (μg.%)	Type III			
			μg.%	% of Total		
1st day	Port wine	400	364	91	100	Trace
2nd day	Amber	51.5	39.14	76	0	0
10 wks.	Amber	16.0	8.0	50	0	0
9 mos.	Amber	1.5	0	0	0	0

* Acknowledgment is made to Dr. C. J. Watson and Miss Violet E. Hawkinson of the Department of Internal Medicine at the University of Minnesota for these porphyrin determinations.

Laboratory Findings.—Examination of the infant's blood at birth showed: Hgb. 16.5 gm./100 cc., RBC 4.8 million/cmm., leucocytes 7.5 thousand/cmm. with 60% lymphocytes and 40% granulocytes. There were 3 erythroblasts/100 WBC. Serologic tests for syphilis were negative for infant and mother; both were Rh positive, type B.

The initial urine passed by the infant was port wine in color; 12 hrs. later it was yellow, and 48 hrs. later it was clear amber. These urine samples, together with specimens of meconium and vernix, were sent to Dr. C. J. Watson to attempt determination of the type and quantity of prophyrins present. Some of the results are shown in Table I. The meconium contained 20.4 mg./100 cc. of coproporphyrin, 17% of this being coproporphyrin III. There was no demonstrable uroporphyrin. The coproporphryin I isolated from the meconium had a melting point of 246° C. Considerable amounts of coproporphyrin I are regularly present in meconium but quantitative data are not available. The amount present in this instance may even constitute a considerable excess.[8] The vernix contained no uroporphyrin and only a trace of coproporphyrin.

Discussion

A review of the literature yields more than 375 cases of porphyria since the condition was first seen clinically by Baumstark in 1874.[9] In reviewing as many of these as were available, only four examples could be discovered where pregnancy occurred while the patient was having active symptoms.[4,10,11] Two of the pregnancies terminated in spontaneous abortions, and two women were pregnant at the time studies were being done, so that outcome was not stated. An additional instance was found in which the initial acute episode immediately followed the birth of an infant.[12] These findings prompt the belief that this is the first infant to have been delivered during an episode of acute porphyria in the mother.

The presence in the infant's urine of coproporphyrin III and uroporphyrin in dwindling amounts following delivery points to a "porphyrinuria" passively acquired through placental transmission. Because the types and relative proportions of pigments excreted by mother and infant were similar, it would be difficult to deny that placental transmission had occurred. The subsequent disappearance of these substances and the infant's failure to develop manifestations of congenital porphyria over the next 11 months are in keeping with this idea. Since the infant does not fit clearly into conventional classifications, the term "passive porphyrinuria" is suggested to describe this new situation. It is recognized, of course, that sufficient time has not elapsed to exclude the possibility of a later appearance of intermittent acute porphyria.

The relation of the symptomatology and pathology of acute porphyria to the defects in porphyrin metabolism are not clear. It has been stated[13] that direct application of porphyrins to the bowel produces spasms which are not relieved by atropine. Mason et al.[14] would explain the gastrointestinal disturbances of acute porphyria on the basis of degenerative changes in the autonomic ganglia. Thorner[15] reports severe multiple neuritis during a course of therapy with hematoporphyrin hydrochloride. Patchy degeneration of the myelin sheaths and axis cylinders of motor nerves and nerve cells, as well as degenerative changes of the cerebral cortex, basal ganglia, cerebellum and spinal cord have been reported.[14]

Although such evidences suggest that porphyrins have direct toxic effects on various tissues, the present case does not support that view. This infant went through embryologic and fetal development in an internal and external environment quite certainly exposed to an excess of these substances. Maternal studies showing increased porphyrin excretion during pregnancy and the presence of abnormal quantities of porphyrins in the urine of the infant at birth indicate that the infant was exposed to them. However, unless it

be the suspected dwarfism, there was never any evidence of untoward effects in the infant. Neurologic or gastrointestinal symptoms were not noted during the time that porphyrins were being excreted, and such symptoms have not subsequently appeared. A normal postnatal developmental schedule and the absence of neurologic abnormalities indicate that damage to the central nervous system probably did not occur. Certainly, if these pigments are important in causing neural degeneration, marked changes were to be expected in the growing brain of the embryo. Absence of such changes in this patient would indicate that pathologic lesions must result in some fashion from the underlying metabolic error rather than from the presence of these pigments. This is suggested also by the relationship porphyrinuria bears to lead poisoning.[16]

Summary

An infant born of a mother suffering from acute porphyria excreted excessive amounts of uroporphyrin and coproporphyrin in the urine during the first few weeks following birth. In the course of the next several months the infant was entirely free from unusual signs or symptoms, except that her stature at 11 months was small. No similar case has previously been recorded. The term "passive porphyrinuria" is suggested to describe this condition.

While an excess of porphyrins in the fetal environment may have resulted in stunting of growth, other evidences in this patient offer support to the belief that the pathologic lesions of porphyria result from the metabolic error and not from the presence of these pigments *per se*.

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SPANISH ABSTRACT

Porfirinuria: Informe de un caso raro

Una niña cuya madre sufría de porfiria aguda, excretó cantidades excesivas de uroporfirina y coproporfirina en la orina durante los primeros días de vida. Durante el transcurso de los meses subsiguientes la niña ha estado libre de síntomas extraordinarios, excepto que a los 11 meses aparece pequeña para su edad. No ha sido informado caso semejante en la literatura médica. El término "porfirinuria pasiva" se sugiere para describir ésta condición.

Apesar de que un exceso de porfirinas en el ambiente fetal puede haber resultado en disminución del desarrollo normal, hay evidencias en ésta paciente para soportar la creencia que las lesiones patológicas que se observan en porfiria, resultan del error metabólico y no de la presencia de éstos pigmentos en sí.

1232 Fifth St.

THE PATHOGENESIS OF FIBROCYSTIC DISEASE OF THE PANCREAS

A Study of 36 Cases with Special Reference to the Pulmonary Lesions

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THE nature of the essential defect in fibrocystic disease of the pancreas is still obscure. The relationship between the pulmonary lesions which are virtually constant findings in patients who survive the neonatal period and the changes in the pancreas has been subjected to much discussion, but as yet no complete agreement has been reached. Although Farber's concept[1,2] of fibrocystic disease as a systemic affection characterized by the production of an abnormal secretion in a variety of glandular organs has found wide acceptance,[3-8] few confirmatory studies have been published.[9] It is the purpose of this report to present pathologic observations bearing on the pathogenesis of the disease and tending to support the theory developed by Farber. Special emphasis is given the findings concerning the respiratory tract because of their clinical implications.

MATERIAL

The study is based on pathologic examination of 36 patients with fibrocystic disease of the pancreas who, with 1 exception,* came to autopsy at the Children's Hospital of Michigan between August 1, 1940 and August 1, 1948. This number represents approximately 2.0% of the total number of autopsies performed on children of all ages up to 13 yrs. during this period. All autopsies reported in this paper were performed under personal supervision of one of the authors and were complete except in cases where restrictions were placed on examination of the cranial cavity.

Figure 1 shows the age incidence of the patients. The sexes were almost evenly distributed. The group consisted of 33 white and 3 Negro infants. The figure of 9% representing Negroes must be compared with that of 35% Negroes in the general hospital population and suggests that the disease is rare in the Negro.

In keeping with the observations of others, a familial incidence was noted in 7 of the 33 families represented by the 36 patients. In 9 cases there were no siblings and 1 patient was an adopted child whose family history was not known. In 2 additional instances the record contained no information concerning siblings.

In each of the remaining 14 families, the siblings, ranging in number from 1 to 8, were apparently healthy. Thus, out of 21 families whose history could be evaluated, 7, or 1/3, had more than 1 child afflicted with fibrocystic disease. Of these 7 families, 4 had had only affected children, usually 2, in one instance 3. The other 3 families had had both healthy and afflicted children in ratios of 60:40, 50:50 and 25:75, respectively.

Clinically, 5 of the patients presented the picture of intestinal obstruction at birth. These were subsequently found to have meconium ileus. Respiratory symptoms dominated the clinical picture in 26 infants, most of whom also showed varying degrees of malnutrition and intermittent or per-

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sistent steatorrhea. Analysis of the clinical records showed no clear-cut division in this case material between patients with predominantly respiratory symptoms and patients presenting the so-called celiac syndrome. The only 2 infants in whom malnutrition, steatorrhea and abdominal distention were early symptoms subsequently developed signs of respiratory disease. Since no distinction could be made on pathologic grounds, the subdivision of the group according to the classification established by Andersen did not seem profitable.

In 3 cases the diagnosis was established at autopsy as an incidental finding in patients dying of acute diseases having shown none of the symptoms customarily associated with fibrocystic disease of the pancreas.

Patients Dying with Meconium Ileus in the Newborn Period

The clinical picture in the five patients of this group was that of intestinal obstruction. No studies of duodenal juice were made. Each infant was subjected to an exploratory laparotomy. In three cases the only abnormalities noted at operation were distention of

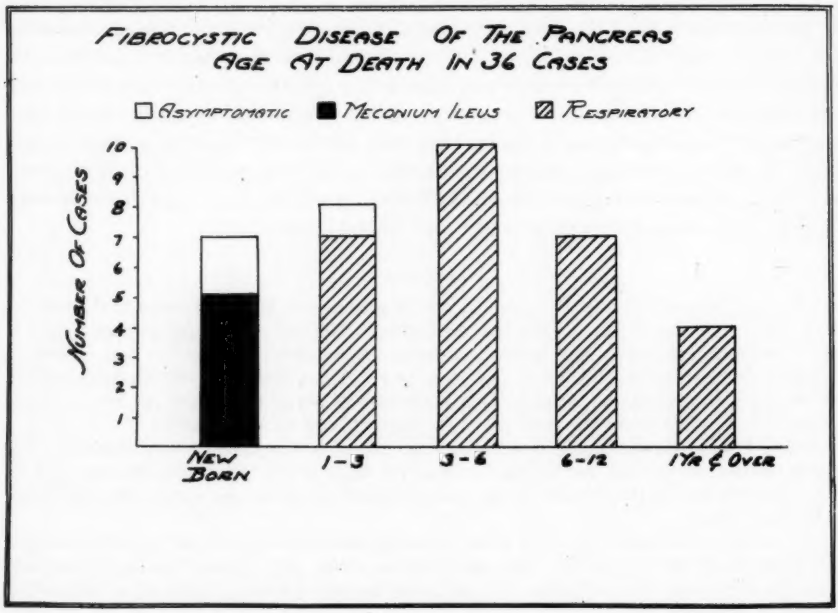


Fig. 1. Age incidence of patients with fibrocystic disease of pancreas.

the small intestine with dark tenacious rubbery meconium and hypoplasia of the colon. In a fourth case multiple adhesions were found between the loops of small bowel indicating that peritonitis had been present in fetal life. The fifth patient was found to have organic atresia of the small intestine; his case will be described in detail later on. All the patients in this group died within a short time after operation.

The gross findings at autopsy were essentially the same as those observed at operation except for the presence of generalized acute peritonitis which had developed postoperatively in each case. Aspiration pneumonia was present in two cases. No gross abnormality of the pancreas was recognized. The duct of Wirsung was not probed because of its

small size. The cystic and common bile ducts were patent and the gall bladder did not appear unusual.

Microscopic examination showed the typical changes in the pancreas as described by Andersen, Farber and others, consisting of inspissation of eosinophilic secretion in the acini and ducts, dilatation of the lumens and atrophy of the lining cells, an increase in intracinar and interlobular connective tissue and mild interstitial cellular infiltrations. While the process in these five cases was clearly prenatal, the changes in the pancreas were of moderate severity as compared to the lesions seen in infants who died later in infancy. This observation is in keeping with the progressive nature of the pathologic process demonstrated by other authors.

There was a dearth of lesions outside the pancreas in this group as compared with the older infants. Except in one case, no changes other than those accounted for by aspiration were found in the respiratory tract. The intestinal glands in four of the five cases did show irregular, occasionally marked dilatation of the lumens by stringy eosinophilic material and formation of microscopic cysts in the mucosa, changes which resembled the lesions in the pancreas. In two cases Brunner's glands in the duodenum also were moderately dilated and atrophic. In one case a section through the gall bladder showed a small cyst in the mucosa filled with stringy mucus-like secretion and lined with flattened epithelial cells. No changes referable to inspissation of secretion were found in the liver. Unfortunately, the salivary glands were not examined in the patients of this group.

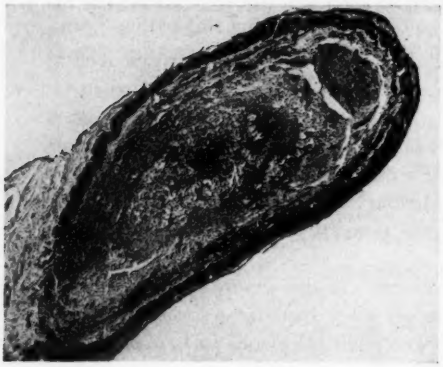
The development of organic intestinal atresia in one infant was of particular interest. Andersen[10] reported the combination of intestinal atresia and cystic fibrosis of the pancreas in two cases but apparently the histologic appearance of the atretic bowel was not studied. Since no similar observations have been recorded, this case deserves a detailed description.

Case Report

Case 1. Baby Girl A. was admitted at the age of 2 days, because of vomiting and enlargement of the abdomen since birth. There was no information concerning the passage of meconium. Physical examination revealed a fairly well hydrated infant with extreme abdominal distention and tympany. No peristaltic sounds could be heard. Rectal examination yielded small amounts of light mucoid material. Patient was vomiting bile-stained fluid. Roentgenologic studies showed markedly distended loops of bowel in which gas seemed mixed with solid material. After injection of barium, the distal half of the colon was visualized and appeared greatly narrowed. Abdominal decompression was attempted and fluids were given by the parenteral route. Exploratory laparotomy was then performed. Proximal small bowel was markedly distended and an atresia in the mid-ileum was found. Below this point the intestinal lumen was narrow and seemed filled tightly with what the surgeon aptly described as "concretions of meconium," so that the bowel did not change its configuration when lifted up. A side to side anastomosis was made and a Wetzel type enterostomy was carried out in the dilated portion of the ileum. In spite of the usual measures, the child died in a shock-like condition 24 hrs. after the operation.

At autopsy, a generalized fibrinous peritonitis was found. Proximal ileum was still distended and contained tenacious meconium. Approximately 40 cm. below the ligament of Treitz, the lumen ended in a blind sac and the continuity of the intestine was maintained by a firm cord measuring 7 mm. in diameter and 8 cm. in length. Transverse sections through this portion disclosed no lumen but the center of the cut surface showed a spherical dark greenish discoloration. Below the atresia the lumen of the bowel was filled with clumps of light greenish tenacious material. Colon was narrow and contained only remnants of barium.

In addition to these findings, incomplete rotation of the colon was demonstrated. Cecum was located in the right upper quadrant and was completely mobile as a result of failure of the mesentery to fuse with the posterior abdominal wall. There was, however, no volvulus or other evidence that the anomalous insertion of the mesentery had caused obstruction.



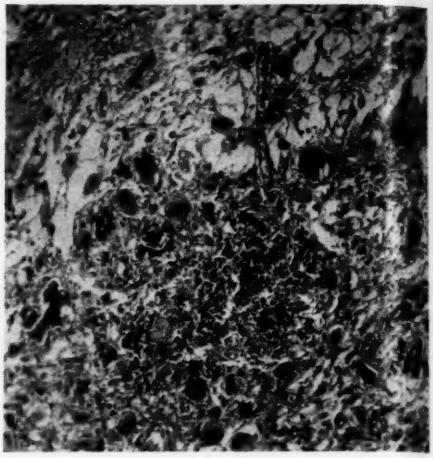


FIG. 2a. Transverse section through atretic portion of ileum in Case 1 showing well formed muscle band, submucosa and obliteration of mucosa and lumen by foreign body reaction. ×13.

FIG. 2b. Higher magnification of central area of Figure 2a showing amorphous debris, deposits of calcium, foreign body giant reaction and granulations indicative of meconium reaction. ×83.

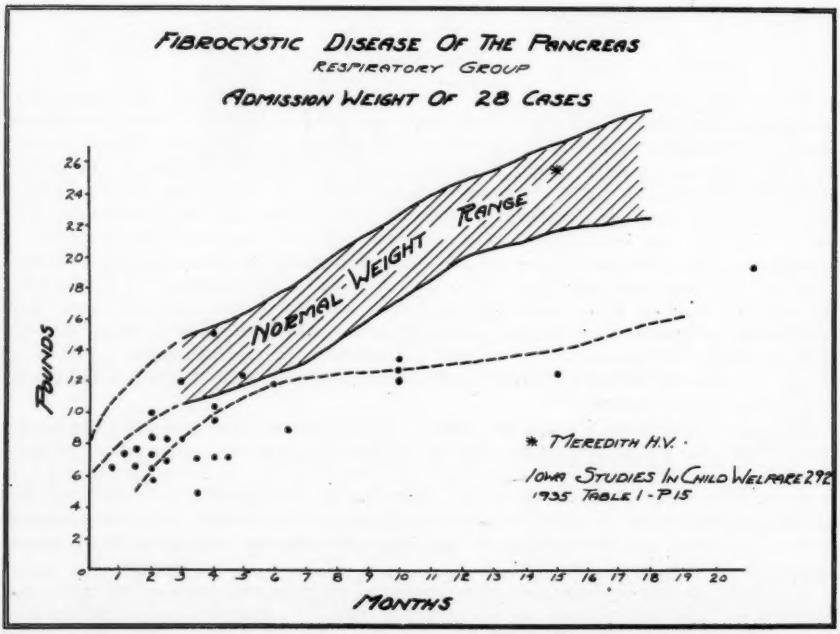


FIG. 3. Weight on admission in 28 cases of respiratory group. Each dot represents patient.

Microscopic examination disclosed the typical findings of fibrocystic disease in the pancreas. The lesions were distinctly more advanced than those in the other 4 cases of meconium ileus. Section through the atretic portion of the ileum showed a striking picture (Fig. 2a and b). Both muscle layers were well developed and formed complete rings around the central area corresponding to the submucosa, mucosa and lumen. This area was the seat of a typical meconium reaction, such as can be seen in the serosa in meconium peritonitis. It was composed of deposits of calcium, amorphous eosinophilic material and stringy mucus-like substance surrounded by numerous giant cells of foreign body type, fibroblasts, occasional hemosiderin-laden macrophages and at the periphery by fibrous connective tissue. No remnants of a lumen or of intestinal epithelium were demonstrable.

Sections through the distal patent portion of the ileum showed frequent dilatation of the intestinal glands with mucus-like material. Mild dilatation of the mucous glands of the trachea was noted and numerous small bronchi contained stringy mucus.

Comment

The unique histologic appearance of the atretic ileum clearly indicates the mechanism of the atresia. The presence of normally formed muscle layers excludes a primary developmental disturbance and the foreign body reaction of meconium type in the center shows that the atresia had resulted from intrauterine impaction of intestinal contents with necrosis of the mucosa and subsequent organization and obliteration of the lumen. Such an explanation for the development of organic atresia in association with fibrocystic disease of the pancreas was rejected by Andersen;[10] this author, however, had not studied the microscopic structure of the atretic bowel. In view of the abnormally viscid character of the meconium found in the absence of pancreatic enzymes, the development of impaction and secondary obliteration is not surprising. The rarity of this occurrence is probably explained by the relatively late onset of the pancreatic changes in utero in most cases of meconium ileus. This assumption is supported by the advanced character of the pancreatic lesion in this patient as compared with the remainder of the group.

Summary of Cases with Meconium Ileus

With one notable exception, the pancreatic lesions in this group were of only moderate severity and extrapancreatic changes were inconspicuous and virtually confined to the alimentary tract. So far as could be determined the complete intestinal obstruction was the result of inspissation of meconium, which in one case had caused secondary organic atresia.

It should be added that one of the five patients was a fraternal twin whose twin brother was entirely free of symptoms of intestinal obstruction and was thought to be normal until he was three weeks old. At that time he began to have a persistent hacking cough and failed to gain weight. He was subsequently admitted to the hospital and a diagnosis of fibrocystic disease of the respiratory type was made and confirmed by typical laboratory findings.

Patients with Predominantly Respiratory Symptoms

The clinical picture observed in the 28 infants comprising this group was somewhat more varied than that of the patients with meconium ileus. The initial symptoms pointed to the respiratory system in 24 instances and usually consisted of a chronic hacking cough which was often spasmodic and had sometimes led to the erroneous diagnosis of pertussis. Sometimes the onset of the illness was described as a cold and in one infant the initial complaint was dyspnea. Failure to gain weight was noted in nearly all these children but was the original complaint in only two additional patients, both of whom began to cough

soon afterward. Vomiting during the neonatal period was recorded in two instances. Both patients shortly had symptoms of respiratory disease. The autopsy in one of these cases disclosed evidence of meconium peritonitis, indicating that the patient had survived meconium ileus with intrauterine obstruction and perforation of the intestine only to die of severe pulmonary disease at the age of two months. A similar episode without peritoneal involvement might well have taken place in the second patient, but this was not proved by the autopsy.

The onset of symptoms referable to the respiratory tract varied in time from the newborn period to the age of 17 months. The vast majority, however, approximately 80%

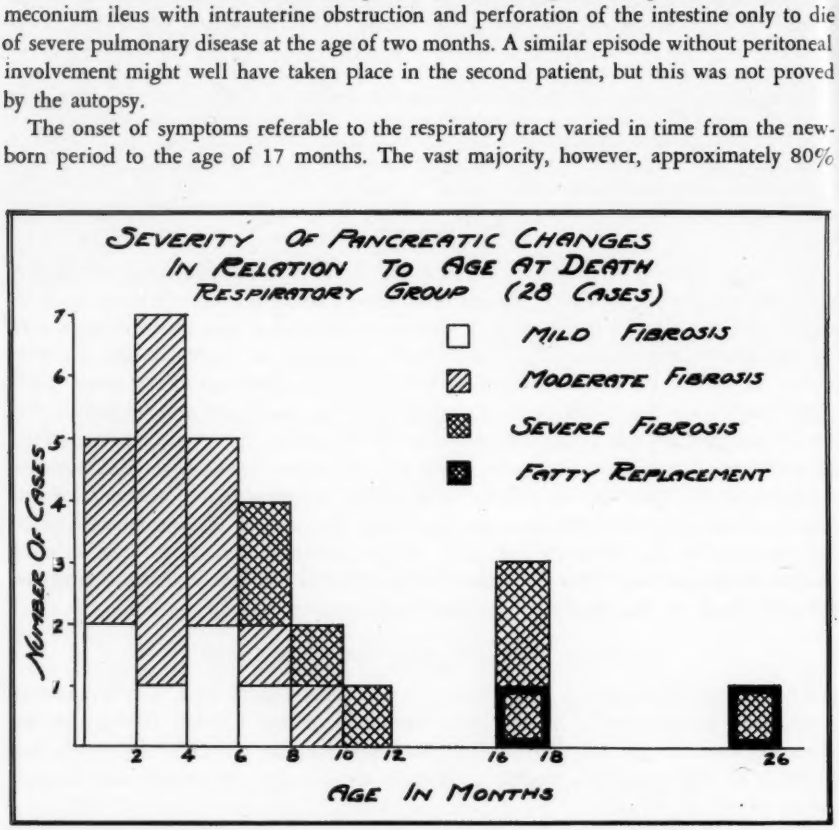


Fig. 4. Correlation between severity of pancreatic fibrosis and length of survival.

of the patients in this group, presented such symptoms before the age of three months. The early onset of respiratory disease suggests that the involvement of the respiratory tract is an integral part of fibrocystic disease paralleling the process in the pancreas, rather than following it as the result of a nutritional deficiency secondary to faulty pancreatic digestion as postulated by Andersen.[3]

Steatorrhea, indicated by bulky, malodorous stools, was noted in the history or observed during the patients' hospital stay in only 13 of the 28 cases and was often intermittent. It was an early symptom in two patients but usually was noted in patients whose respiratory symptoms had developed after the age of three months. Often it did not become apparent until weeks or months after the onset of other manifestations.

Although most of the patients had a ravenous appetite, their nutritional state was poor in all but four instances. A lag in weight gain was apparent from the start in all those

infants whose record gave adequate information on this point. In general, the older the patients the less favorably did their weights compare with average normal values (Fig. 3). By contrast, body length was by no means constantly affected and even many infants beyond the age of four months failed to show significant deviations from normal standards for height.

The physical findings were otherwise meager. Occasionally moderate abdominal enlargement was recorded. Auscultation of the thorax revealed rales or rhonchi in 21 cases. Diminution of breath sounds was noted twice. The percussion note was hyperresonant in a few patients and impaired in a few others. In seven infants the initial examination disclosed no abnormal signs related to the lungs even though the children had a hacking cough and roentgenograms might show abnormalities in the lung fields. Nearly every infant had an elevated temperature.

Studies of the duodenal juice were carried out only in those patients who were admitted after 1942 so that the data on tryptic activity are available for only 13 cases. In 12 of these no trypsin could be demonstrated. In the 13th case, the first examination indicated a tryptic activity of 20% by the modified Fermi method[11] but a second test later showed no activity.

Oral glucose tolerance tests were done in nine cases and showed a typical "flat" curve.

The leukocyte counts were usually, though not always, elevated, ranging from 10 thousand to 40 thousand in 75% of the cases.

Throat cultures were obtained from 23 patients and yielded coagulase positive Staph. aureus in six, Str. hemolyticus in five and nonhemolytic streptococci in two cases. No pathogenic organisms were demonstrable in 10 instances.

Roentgenograms of the chest usually showed emphysema and often central pulmonary infiltration. Later in the course of the disease, patchy areas of pneumonic infiltration were often noted and occasionally consolidation of lobar type was present. In four patients the initial roentgenograms showed no abnormality but, in all of these, later films disclosed signs of pulmonary disease.

The course and duration of the illness varied considerably depending somewhat on the initial condition of the patient and the treatment. Until 1942 the correct diagnosis was rarely made and treatment was largely confined to the administration of sulfonamides and supportive measures. After 1943, when penicillin became available, both injection and inhalation therapy with this drug was used. Pancreatin was usually given and the treatment essentially followed the outline given by Andersen.[12, 13]

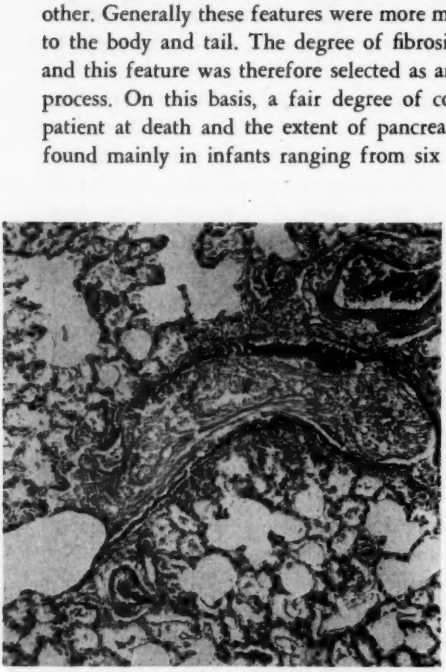
The clinical course of the illness was characterized by slowly progressive weight loss, irregular fever and general decline. In most patients dyspnea became a prominent symptom and was accompanied by attacks of cyanosis and inspiratory retraction of the chest wall. The obstructive character of the breathing was striking in many cases and these patients seemed to die of slow suffocation unrelieved by oxygen therapy.

The pathologic changes associated with fibrocystic disease have been fully described by Andersen and by Farber and, since the findings in this study are in essential agreement with their observations, only a few pertinent observations shall be made.

In this group gross abnormalities of the pancreas were frequently recognized and consisted in increased firmness, hyperemia and sometimes irregularities of the surface caused by small nodules or cysts filled with thick white material. Gross demonstration of the duct of Wirsung was invariably unsuccessful.

The microscopic appearance of the pancreas was more varied than in the first group.

Even within the individual organ there was often marked variation in the amount of inspissated secretion and the degree of dilatation of ducts and acini from one area to another. Generally these features were more marked in the head of the pancreas as compared to the body and tail. The degree of fibrosis was much more uniform within each gland and this feature was therefore selected as an arbitrary index of the severity of the disease process. On this basis, a fair degree of correlation was found between the age of the patient at death and the extent of pancreatic involvement (Fig. 4). Mild changes were found mainly in infants ranging from six weeks to six months in age but were seen as



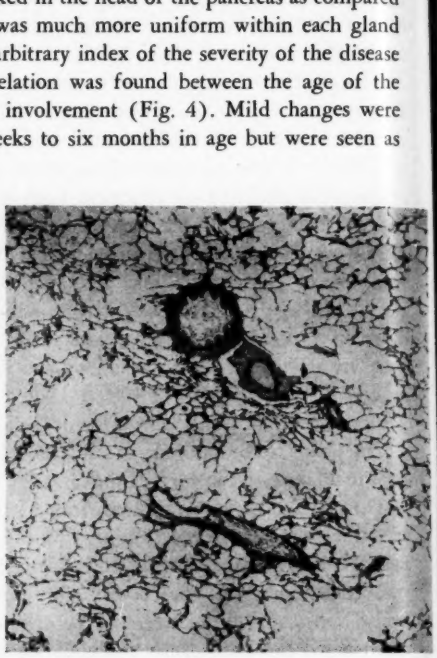


FIG. 5. Terminal bronchiole obstructed with stringy mucoid secretion. ×83.
FIG. 6. Emphysema secondary to obstruction of mucus-filled bronchioles. Note absence of inflammatory changes. ×27.

late as eight months. Moderately severe lesions were encountered as early as eight weeks and predominated up to the age of six months. Thereafter severe changes began to be seen and in infants older than 10 months the process was always marked. Fatty infiltration and replacement of the parenchyma was found only in the two oldest patients, aged 18 and 26 months, respectively.

These findings corroborate again the progressive nature of the process and are in accord with the sequence of changes observed in experimental obstruction of the pancreatic duct leading from atrophy and progressive fibrosis to fatty replacement.[14] Mild changes therefore would seem to signify a recent onset of the process and their occurrence as late as six to eight months would suggest that the disturbance is not always present at birth but may develop in infancy, as postulated by Farber.[15]

Proof that the obstructive lesion in the pancreas was not the result of primary atresia or stenosis of the duct of Wirsung was established in only one case in which serial sections were made through the head of the pancreas and an adequate lumen was demonstrated from the duodenal orifice backward for a distance of approximately 2 cm. In most of the

other cases a well developed duct could be seen in routine sections of the head or body of the organ. Both Andersen[10] and Farber[2] have observed typical changes in accessory pancreatic tissue, a finding which could not be explained by an isolated atresia of the main pancreatic duct.

In every case of this group, lesions outside the pancreas were encountered. Involvement of the respiratory tract was constant. The typical picture was one of severe obstructive emphysema and atelectasis due to the presence of tenacious mucopurulent, rarely mucoid exudate in the air passages of all calibers and usually but not always accompanied by more or less widespread bronchopneumonia, bronchiolectasis and bronchiectasis. A tentative diagnosis of fibrocystic disease was often made on the basis of these findings alone which seemed almost pathognomonic for this age group. Enlargement of the hilar pulmonary and peribronchial lymph nodes was nearly always present. Cultures of the lungs yielded coagulase positive staphylococcus aureus in 22 cases. In three others Staph. albus, Ps. aeruginosa and A. faecalis, respectively, were cultured while no growth was observed in the remaining three instances.

The microscopic appearance of the lungs corresponded to the gross picture and varied from simple obstructive emphysema and atelectasis due to plugging of the bronchioles with stringy mucus to extreme chronic pneumonitis with destruction of bronchial walls and abscess formation. The evolution of the pulmonary lesion was studied in detail. The observations seemed conclusive evidence that the essential change consists in the production of thick mucus by the bronchial and tracheal glands which accumulates in the air passages and cannot be expelled. This process seems analogous to the disturbance in the pancreas, as Farber has emphasized.

The plugging of the bronchi and bronchioles with secretions was the earliest change observed and was invariably associated with emphysema and atelectasis (Figs. 5 and 6). The bronchial walls had remained intact, inflammatory changes were as yet absent and no squamous cell metaplasia of the respiratory epithelium was found. This was the picture seen if the patient died early in the course of the disease or if infection of relatively short duration had been controlled by antibiotic therapy, and was encountered in three of the patients. More often the purely obstructive changes were already combined with inflammatory lesions indicative of secondary infection. The exudate in many air passages had now become purulent and infiltration of their walls with inflammatory cells and thickening had begun (Fig. 7). There could still be found, however, many bronchioles of normal appearance except for the presence of mucus in the lumen. As the inflammatory changes progressed, fewer and fewer of these purely obstructive changes could be found and increasing thickening of the bronchial walls, inflammatory cell infiltration and extension of the exudate into the peribronchial alveoli became the outstanding features (Figs. 8, 9 and 10). Finally, the bronchial lumens were dilated, the walls were destroyed, bronchiolectatic abscesses had formed and the pneumonic foci had become confluent. By this time the inflammatory lesions completely overshadowed the original changes. The severity of the inflammatory process generally paralleled the duration of the symptoms.

Dilatation of the mucous glands in the trachea and bronchi with flattening of the epithelium and outpouring of secretion from the ducts was commonly seen, even in cases in which there was little or no local inflammatory reaction (Fig. 11).

Farber[2] explains the suppurative lesions in the respiratory tract on the basis of secondary infection supervening and persisting in air passages chronically filled with tenacious

secretions which cannot be drained adequately. This study of the evolution of the pulmonary changes and especially the demonstration of the "pure," uncomplicated obstructive lesions strongly support this concept.

As a corollary to the view that abnormal production of secretions in the air passages is the basic disturbance in the respiratory system, the role of respiratory obstruction in fibrocystic disease of the pancreas must be emphasized. The factor of obstruction, which cannot be as readily controlled as infection and nutrition, is an essential feature of the disease and can be in itself the chief clinical problem and ultimate cause of death. This was illustrated by the case histories of three of the patients who died of respiratory obstruction, although at the time of death no trace of infection could be found. Only one of these cases is presented in detail, but the others were entirely similar.

Case Report

Case 2. T. D. was admitted at the age of 2 mos. because of a cough present since shortly after birth and increasing in severity. Breathing had been labored almost from the start. Appetite had been excellent until a few days before admission. Weight had risen from 2.9 kg. at birth to 3.2 kg. at the age of 6 wks. and had fallen to 3.1 kg. by the time of admission. Stools had always been malodorous.

Family history was negative at this time. Subsequently, the parents had another child who was admitted to the hospital with complaints similar to those of his brother, and who died with fibrocystic disease of the pancreas. Autopsy confirmed the diagnosis and the case is included in this study.

Patient on admission was poorly nourished and irritable. He had a paroxysmal, nonproductive cough followed by transient cyanosis. Pharynx contained thick tenacious mucus. Lungs were thought to be normal with respect to physical signs. Abdomen was not appreciably distended. Temperature was 37.0° C.

Urinalysis was negative. Blood hgb. 13.2 gm./100 cc., WBC count 12.1 thousand with a differential count of 15% leucocytes and 85% lymphocytes. Intradermal tuberculin test was negative. Cough plates for H. pertussis yielded no growth. Roentgenograms of the chest showed marked pulmonary emphysema without evidence of atelectasis or consolidation.

Under observation the child ate hungrily but his weight remained stationary. Temperature was normal almost throughout the remainder of his life. Stools were described as soft, yellow and "mushy" but not malodorous or bulky. Cough persisted, became increasingly severe and frequent, and was often associated with cyanosis.

Therapy consisted at first of oral administration of sulfadiazine and small amounts of whisky. For a short period, benadryl was given without benefit. Twelve days after admission the child was placed in an oxygen tent and received inhalations of penicillin aerosol. Laryngoscopic and bronchoscopic examinations were done on the 16th hospital day. The operator described the lumen of the trachea as narrow and the lining as dry. Neither the introduction of the bronchoscope nor the local application of adrenalin seemed to improve the respiratory obstruction. Cultures of the material obtained during the procedure were sterile.

Following bronchoscopy the child was placed in the steam room and oxygen was again given, but for a few days his condition was critical. Respirations became extremely labored and there was inspiratory retraction of the intercostal spaces and intercostal areas. An inspiratory crow developed. After 5 days the child's condition improved somewhat and it was possible to discontinue the oxygen therapy and remove him from the steam room.

During the 4th week in the hospital the child was in good enough condition to undergo an examination of the duodenal juice. Tryptic activity was found to be completely absent in an alkaline specimen. An oral glucose tolerance test showed a fasting blood sugar level of 50 mg./100 cc. (values corrected for so-called true sugar) with delayed rise to a maximum of 110 mg./100 cc. in 2 hrs.

Patient was given pancreatin and a special formula containing excess casein. Later, the formula was changed to a mixture of lactic-acid skimmed milk supplemented by amino-acids and glucose. A preparation of multiple vitamins was given in large doses. Although he continued to eat hungrily and received a formula containing 150 cal./kg. body weight, he failed to gain. Another episode of severe respiratory distress occurred at the end of the 6th hospital week. The respirations became wheezing and rales and rhonchi were audible throughout both lung fields. Again there was temporary

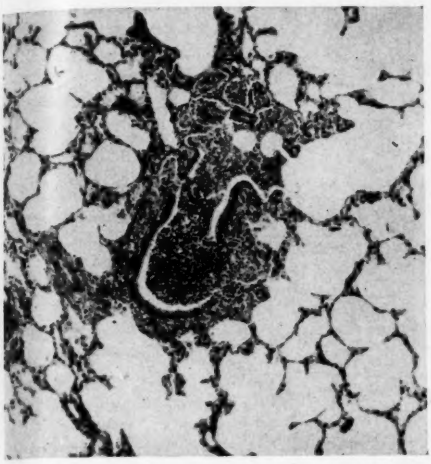


FIG. 7. Early inflammatory changes. Purulent exudate in bronchiole and few adjacent alveoli. Slight thickening and cellular infiltration of bronchial wall. ×83.

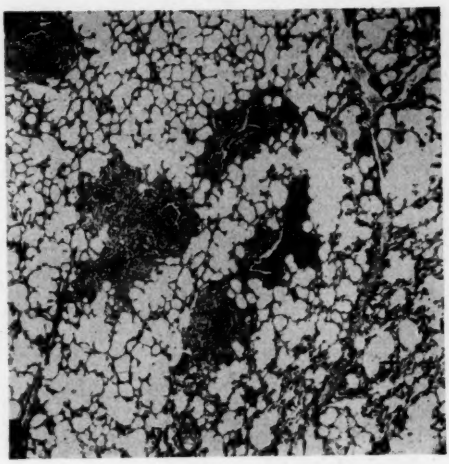


FIG. 8. More marked inflammatory changes. Suppurative bronchiolitis with increase in size of pneumonic foci. ×22.

FIG. 9. Further progress of inflammatory process. Marked peribronchial thickening. ×11.

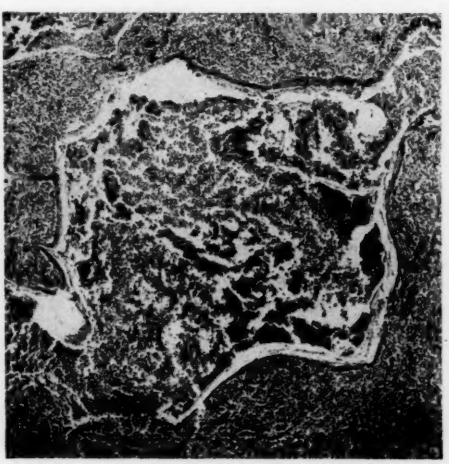


FIG. 10. Extreme degree of bronchial inflammatory changes. Lumen filled with purulent exudate. Lining partly ulcerated; shows extensive squamous cell metaplasia. Walls greatly thickened and densely infiltrated; marked bronchiectatic dilatation. ×27.

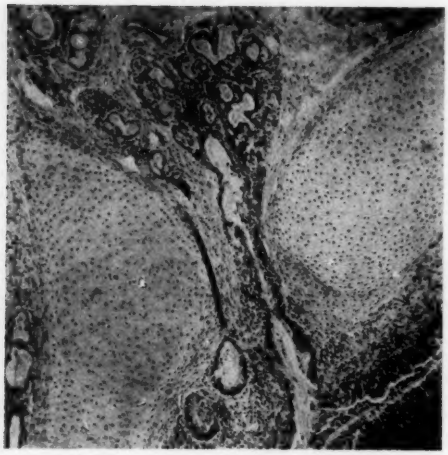


FIG. 11. Changes in bronchial mucous glands. Note dilatation of lumens with inspissated secretion and atrophy of lining epithelium. ×79.

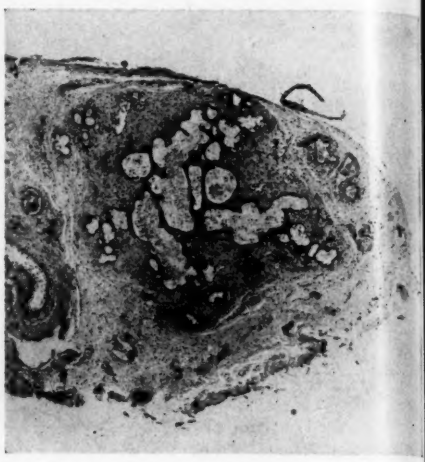


FIG. 12. Cross section through cystic duct showing multiple spaces lined with atrophic flattened epithelium and filled with inspissated secretion. ×32.

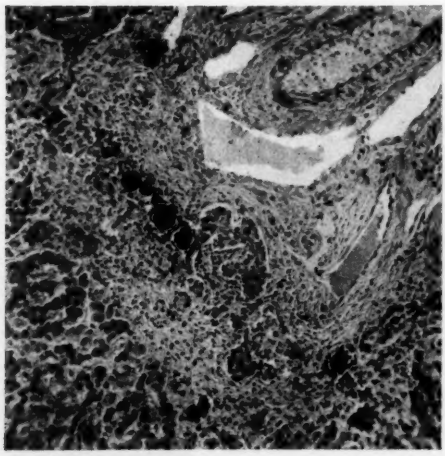


FIG. 13. Portal area in liver showing numerous small bile ducts distended with dense eosinophilic secretion and mild inflammatory cell infiltrations in surrounding stroma. ×91.

improvement following steam therapy but the child was now extremely weak and emaciated. Marked air hunger again developed shortly and the child died in a shock-like state 45 days after admission at the age of 3½ mos.

At autopsy the lungs were emphysematous in their anterior portions. Posteriorly and in patchy areas anteriorly there were areas of atelectasis. Large bronchi and the trachea appeared dry and empty. From the cut surface of the smaller bronchi a clear thick gray mucoid exudate was easily expressed. Culture of the lung postmortem yielded coagulase negative Staph. aureus, probably a contaminant since smears and sections showed no organism. Pancreas weighed 5 gm. and did not seem grossly abnormal. Liver was somewhat atrophic. Gall bladder appeared small but the lumen contained brown bile which was readily expressed into the duodenum through the cystic and common ducts.

Microscopic examination of the pancreas showed the typical lesions of fibrocystic disease developed to a moderate degree of severity. Brunner's glands in the duodenum showed marked dilatation of their lumens with a pale stringy secretion. Mucous glands in the pharynx, upper esophagus and trachea were often dilated and filled with abundant mucus.

Lungs were entirely free of inflammatory changes. Lumens of the smaller bronchi were plugged with stringy mucoid exudate. Focal extravasations of red blood cells were found in the alveoli. In addition, emphysema and atelectasis were seen in variable combination in all sections examined. No evidence of epithelial metaplasia was discovered either in the respiratory tract or in other epithelium-lined passages.

Comment

Both the clinical picture and the pathologic findings in this case representative of a group of three patients indicated severe respiratory obstruction as the outstanding feature and immediate cause of death. Infection had been prevented by the use of antibiotics. The patient's nutritional state was poor but no evidence for a specific deficiency was uncovered and malnutrition was not per se the cause of death in this child. A similar case has been reported by MacGregor and Rhaney.[16]

Squamous cell metaplasia of epithelium was found in the trachea and bronchi in only 15 of the 28 cases comprising the respiratory group. It was never seen outside the respiratory tract although it was searched for in the lining of the renal pelves, ureters, bladder and other locations. The metaplasia of respiratory epithelium was always irregular in distribution and often only a few small metaplastic areas could be found although in a few cases the process was extensive. The presence of metaplasia could not be directly correlated with the age of the patients or the duration of symptoms. It was a constant finding in patients surviving beyond the age of 10 months but was occasionally seen as early as six weeks. Metaplasia was never found in bronchi which did not also show severe inflammatory changes. On the other hand, chronic inflammation was by no means constantly associated with metaplasia.

Squamous cell metaplasia of respiratory epithelium in fibrocystic disease has been widely accepted as prima facie evidence of avitaminosis A and from this premise the further conclusion was drawn that avitaminosis A alone or in conjunction with other nutritional defects played a major part in the genesis of the pulmonary lesions.[3] Poor absorption of vitamin A from the intestine has been amply demonstrated in this condition and it is therefore impossible to exclude a general deficiency in vitamin A as a factor in the production of squamous cell metaplasia in all cases. This is not to say, however, that localized metaplasia is necessarily an expression of generalized avitaminosis. In the majority of cases the observed facts favor the role of local rather than general factors in the production of this lesion. The occurrence of metaplasia in early infancy speaks against a nutritional origin since such changes could not be expected to be seen much earlier that at six months if they developed on the basis of an acquired deficiency. In cases of congenital biliary atresia in which absorption of fat-soluble vitamins is also

impaired, Altshule[17] was unable to find squamous cell metaplasia unless the patient had survived for at least six months.

The absence of rickets in this material as in that of other studies further argues against the role of vitamin A deficiency in producing metaplasia in the average case. When the absorption of fat-soluble substances is interfered with, the two deficiency states usually develop in a parallel manner. Andersen[8] explained the virtual absence of rickets in fibrocystic disease on the basis of failure to grow. As previously mentioned, the growth in length of the patients in this study was by no means constantly retarded and even among the older and severely malnourished infants many compared favorably with normal children of the same age in regard to body length.

Finally, metaplasia was not a constant finding, was never generalized and was never found in the absence of infection. On the other hand, it does occur in association with chronic inflammatory lesions in patients with normal pancreatic function whose intake and absorption of vitamin A are presumably adequate.[18]

In view of these arguments, it may be concluded that squamous cell metaplasia in patients with pancreatic fibrosis usually arises on the basis of local factors of which chronic inflammation would seem the most important. Vitamin A deficiency undoubtedly plays an important part in the total clinical problem of fibrocystic disease, especially in the advanced cases, but there is no evidence that the development of the pulmonary lesions depends on a nutritional defect. Andersen herself,[3] the chief proponent of the latter view, states that dietary deficiency in vitamin A does not lead to purulent bronchitis or pneumonia and assumes additional nutritional defects to explain the changes in the respiratory tract. Without underrating the importance of nutritional deficiencies developing in the course of fibrocystic disease, our findings seem conclusive evidence that the involvement of the respiratory tract is an integral part of the disease which develops parallel with, not secondary to, the nutritional failure and depends on a basic abnormality of secretory processes predisposing to secondary infection.

Aside from the changes in the respiratory tract, lesions outside the pancreas were encountered in all but one case, that of a seven month old child who succumbed to severe pulmonary infection but whose pancreas showed only mild changes. Of the 28 cases in this group, 85% had changes in the gastrointestinal tract consisting of dilatation of glandular structures with mucus and atrophic flattening of the lining cells. This change was most marked and most often seen in the Brunner's glands of the duodenum and in the mucous glands of the esophagus.

Next in frequency were changes in the biliary passages, noted in 60% of the cases. The gall bladder in these patients was small, shrunken and gray in color with thickened walls and an almost solid opaque stringy colorless mucus filling the lumen. This picture when present we consider as pathognomonic of fibrocystic disease. The cystic duct connected with a gall bladder of this type was invariably occluded although the common duct was patent in all cases.

The microscopic study of the gall bladder showed many dilated cyst-like glands and crypts in the depth of the mucosa, lined by flattened epithelium and filled with mucus. The lining of the intimal surface itself was irregularly flattened and deformed. Inflammatory changes were absent.

Transverse sections were made through the obliterated cystic duct in several instances. In each case these showed, in place of a single patent lumen, multiple epithelium-lined spaces resembling entirely the crypts in the wall of the gall bladder and like them containing mucus (Fig. 12).

These findings indicate a secondary process of obliteration rather than a true malformation and support in this respect the view expressed by Andersen.[3]

Striking lesions in the liver attributable to inspissation of secretion in the intrahepatic biliary passages (Fig. 13) have been described by Farber.[2] In the material in this study, gross cirrhosis was not present. Microscopic study showed focal but definite dilatation of small bile ducts with inspissated eosinophilic material and fibrosis of the adjacent parenchyma in two cases. Evidently the process does not often involve the secretory action of the liver.

In contrast to the experience of Farber, no convincing changes were found in the salivary glands in the 18 cases of this material in which these organs were examined. In one case a single area of acinar dilatation with inspissation of secretion and slight increase in connective tissue was discovered in an otherwise normal appearing gland.

Summary of Cases with Respiratory Disease

Mild, moderate and severe changes were found in the pancreas in this group, suggesting a variable time of onset of the disturbance. The respiratory tract was involved in every instance. In early cases or in patients whose infections were brought under control, purely obstructive changes had resulted from the presence of tenacious mucus. A progressive chronic suppurative process was demonstrable in the other cases and the evolution of these lesions corresponded with the duration of the process. Squamous cell metaplasia was absent in over 50% of the patients and when present was an isolated lesion which could not be regarded as proof of a general deficiency in vitamin A. The nutritional state of most of the patients was poor but rickets was not encountered even though growth in length was not consistently retarded. Changes in other organs considered to be analogous to those in the pancreas were found in a high percentage of the cases. The gastrointestinal tract and the biliary system were most commonly involved.

Patients in Whom the Pancreatic Changes Were Incidental Findings

This group consisted of only three infants, all of whom were admitted for seemingly unrelated conditions. All were newborn infants. One patient died at the age of 13 days with thrombosis of cerebral vein and massive cerebral hemorrhage; the other two suffered from severe epidemic diarrhea. There had been no symptoms referable to pancreatic insufficiency or to pulmonary disease. The autopsy findings were related to the main illness in each case and no gross abnormalities suggestive of fibrocystic disease were noted. Microscopic examination showed typical but always mild changes in the pancreas which could be clearly differentiated from syphilitic pancreatitis and from the changes in the pancreas associated with uremia recently described by Baggenstoss.[19] No lesions outside the pancreas attributable to fibrocystic disease could be found in two cases. In the third patient, dilatation of mucous glands with excessive amounts of mucus in the lumen was noted in trachea and esophagus.

The cases in this group apparently represent the incipient stage of the disturbance. In view of the controversy regarding the postnatal onset of the disease in some cases, it is interesting to note that the only patients with early asymptomatic lesions were infants who died in the newborn period. In a large autopsy material in which microscopic examination of the pancreas was done as a routine procedure, no distinct lesions have been encountered in infants beyond the age of one month unless the patient had shown clinical evidence of the disease. Mild focal inspissation of secretion in the pancreatic

acini was a common finding but such cases were not included in this study because of the lack of definite criteria.

No observations have been made which could shed light on the mechanism responsible for the abnormal secretory process in fibrocystic disease of the pancreas. In view of the familial incidence of the condition, a genetically determined abnormality in the composition of enzymes or other substances present in the secretion of the affected organs seems the likeliest explanation but there seem to be as yet no studies bearing on this point.

Summary and Conclusions

Pathologic studies and clinical data from 36 fatal cases of fibrocystic disease of the pancreas support the concept that the basic pathologic process consists in an anomaly of secretory function and frequently involves other glandular structures besides the pancreas—notably the respiratory tract, the intestinal tract and the biliary system.

The development of fixed organic lesions in the affected organs was found to be variable and to depend to some extent on the time factor. Extrapancreatic lesions were rare and inconspicuous in infants dying in the newborn period, whereas, in patients who had survived the newborn period, involvement of the respiratory tract was constant and changes in other systems were commonly encountered. Variations in the intensity of the pancreatic changes suggested the possibility of a postnatal onset of the process in some cases.

Inspissation of abnormally viscid meconium in the small intestine was the sole demonstrable cause of complete intestinal obstruction in four of the five patients dying with meconium ileus in the newborn period. It was shown however that inspissation of meconium as part of the disease process can lead to secondary obliteration and organic atresia of the intestine in utero. Evidence was presented to show that the atresia of the cystic duct frequently encountered in older infants is due to a similar process of secondary obliteration.

A detailed study of the pulmonary lesions encountered in 28 patients with respiratory symptoms indicated that the original pathologic process in the lungs is analogous to that in the pancreas and consists in an accumulation of viscid secretion in the air passages. The resulting state of respiratory obstruction is an important component of the disease process which by itself can lead to death. This point was illustrated by a representative case history. The respiratory tract, being, in contrast to the pancreas, accessible to bacterial invaders, usually becomes the seat of secondary infection which is perpetuated in the presence of inadequate drainage from the plugged air passages and leads to progressive inflammatory changes.

No evidence for a primary nutritional factor in the genesis of the pulmonary changes was found. The conclusion was reached that nutritional deficiencies play a secondary though clinically important part in the evolution of the disease process.

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SPANISH ABSTRACT

La Patogénisis de la Enfermedad Fibrocística del Pancreas

Los estudios patológicos y los datos clínicos de 36 casos fatales de la enfermedad fibrocística del pancreas sostiene el concepto de que el proceso patológico básico consiste en una anomalía de función secretoria y frecuentemente involucra otras estructuras glandulares además del pancreas—especialmente la vía respiratoria, la vía intestinal y el sistema biliar.

Se encontró que el desarrollo de lesiones orgánicas fijas en organos afectados varía, dependiendo hasta cierto punto en el factor de tiempo. Las lesiones extrapancreáticas fueron raras e inconspicuas en infantes que murieron acabando de nacer, mientras que en pacientes que pasaron ese período, la complicación de la vía respiratoria era constante y los cambios en otros sistemas se encontraron muy amenudo. Las variaciones en la intensidad de los cambios pancreáticos sugerieron la posibilidad del comienzo postnatal del proceso en algunos casos.

La inspisación del meconio anormalmente viscoso en el pequeño intestino fué la única causa demostrable de la completa obstrucción intestinal en cuatro de los cinco pacientes que murieron de meconium ileus en el período inmediatamente después del nacimiento. Se demostró, sin embargo, que la inspisación del meconio como parte del proceso de la enfermedad puede conducir a obliteración secundaria y a astresia orgánica del intestino en útero. Se presentaron pruebas para demostrar que la atresia del conducto cístico que se encuentra frecuentemente en infantes mayores se debe a un proceso similar de obliteración secundaria.

Un estudio detallado de las lesiones pulmonares que se encontraron en 28 pacientes con síntomas respiratorios indicaron que el proceso patológico original en los pulmones es análogo al del pancreas y consiste en una acumulación de secreción viscosa en los pasajes de aire. El estado que resulta de la obstrucción respiratoria es un componente importante del proceso de la enfermedad que en sí puede llevar a la muerte. Este punto fué ilustrado por un caso histórico representativo. La vía respiratoria, siendo, en contraste con el pancreas, accesible a invasores basteriales, generalmente se vuelve el asiento de infección secundaria que se perpetua en la presencia del drenaje inadecuado de los pasajes de aire tapados y conduce a los cambios inflamatorios progresivos.

No se encontró prueba para un factor nutritivo en la génesis de los cambios pulmonares. Se llegó a la conclusión de que las deficiencias tienen una parte secundaria aunque clinicamente importante en la evolución del proceso de la enfermedad.

5224 St. Antoine St.

CYCLIC NEUTROPENIA IN AN INFANT

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CYCLIC neutropenia, one of the rarer types of agranulocytic angina,[1] is characterized by recurrent periods of marked neutropenia occurring at intervals of approximately three weeks, and persisting for many months or years, while the usual acute form is manifested in a single fulminating episode.

A review of the literature revealed a total of six cases of cyclic neutropenia. Five of these occurred in adult women.[2-6] The sixth, a male, acquired the disease in infancy, and the periodic episodes continued until his death from bronchopneumonia 34 years later.[7-10]

This case, the second to be reported having its onset in infancy, has persisted for more than two years. The infant was admitted to the hospital during her initial attack, and has had three subsequent admissions. She has been under care on the ward for almost 12 months.

CASE REPORT

E. P., a 5 mo. old white female, was first admitted with a history of fever, multiple skin lesions, pulling at her ears, vomiting, and irritability of 3 days' duration. About 3 wks. prior to these complaints, her mother noticed several scattered skin lesions (similar to those present on admission) which were treated in the outpatient department, and which healed with local therapy after several days.

Labor and delivery were uneventful; she weighed 3.6 kg. at birth. Family history was completely negative.

Examination revealed an acutely ill infant with a temperature of 39.8° C., a right purulent otitis media, and many furuncles scattered over her back. Heart and lungs were normal. Liver and spleen were not palpable, and the lymph nodes were not unduly enlarged. She weighed 7 kg.

While on the ward she had 3 episodes of hyperpyrexia, each associated with an acute infection and extreme neutropenia, the neutrophils disappearing entirely from the peripheral blood on one occasion (Fig. 1). Initial and subsequent infections and fever lasted 5 to 7 days. Although usually active and alert, she became irritable and listless when she developed fever. She was discharged on the 46th day of hospitalization.

Roentgenograms of the mastoids were suggestive of a cholesteatoma of the right mastoid. Hemoglobin, erythrocyte count, and the percentage of eosinophil and basophils were within normal limits. Ten to 20% monocytes were found frequently when the neutrophils were markedly depressed. Two blood cultures were sterile. Repeated swabs of the aural discharge cultured a mixed bacterial flora, while cultures from the skin lesions revealed Staph. aureus. Urinalysis failed to show sugar, albumin or abnormal cellular elements.

Therapy consisted of sulfathiazole 5% ointment to the skin lesions, enteral sulfadiazine and sulfathiazole, and parenteral pencillin; there was no apparent effect on the disease.

The patient entered the hospital for the 2nd time 4 mos. later, with a history of cough of 11 days' duration. Two wks. prior to admission her right ear began to drain.

She was moderately toxic and irritable. She was well developed and weighed 8.6 kg. A right purulent and left catarrhal otitis media and a pharyngitis were found. Medium fine rales were audible over the right thorax. Liver and spleen were not eniarged.

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(Received for publication Sept. 20, 1948.)

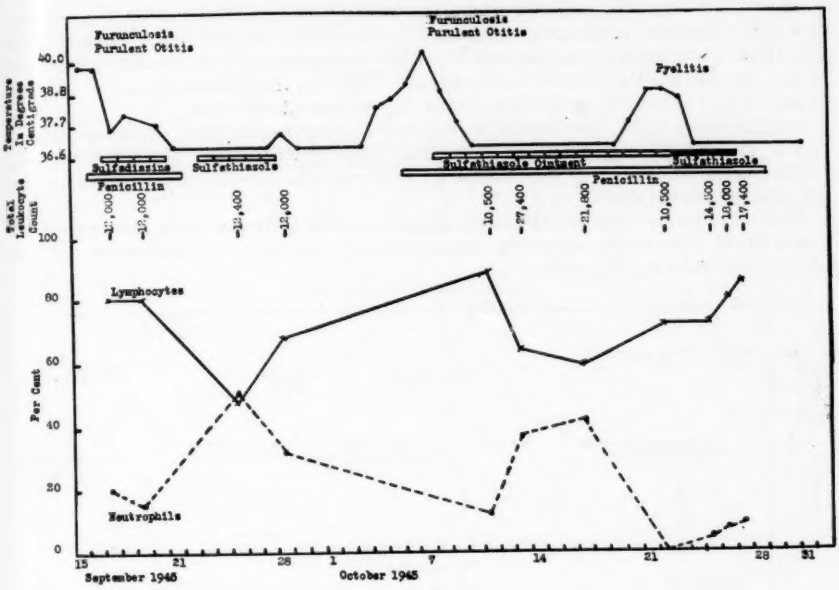
Furunculosis
Furulent Otitis
Furunculosis
Furulent Otitis
Pyelitis
Temperature In Degrees Centigrade
40.0
38.8
37.7
36.6
Sulfadiazine
Penicillin
Sulfathiazole
Sulfathiazole Ointment
Sulfathiazole
Penicillin
Total Leukocyte Count
-12,000
-13,000
-12,400
-12,000
-10,500
-27,400
-21,800
-10,500
-14,500
-19,000
-17,400
100
80
60
40
20
0
Per Cent
Lymphocytes
Neutrophils
15
21
28
1
7
14
21
28
31
September 1945
October 1945

FIG. 1

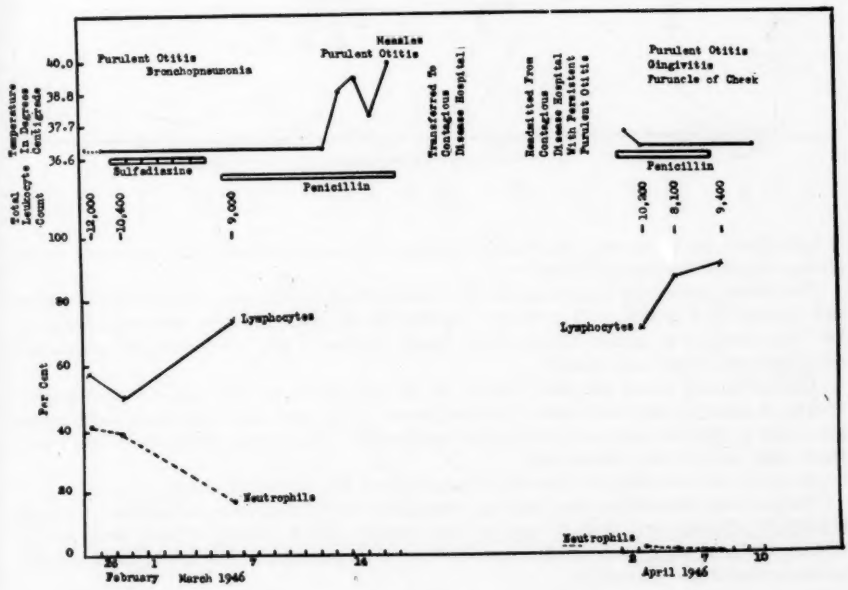
Purulent Otitis
Bronchopneumonia
Measles
Purulent Otitis
Transferred to Contagious Disease Hospital
Readmitted From Contagious Disease Hospital With Persistent Purulent Otitis
Purulent Otitis
Gingivitis
Furuncle of Cheek
Temperature In Degrees Centigrade
40.0
38.8
37.7
36.6
Sulfadiazine
Penicillin
Penicillin
Total Leukocyte Count
-12,000
-10,400
- 9,000
-10,200
- 8,100
- 9,400
100
80
60
40
20
0
Per Cent
Lymphocytes
Neutrophils
Lymphocytes
Neutrophils
26
1
7
14
2
9
16
February
March 1946
April 1946

FIG. 2

About 3 wks. later, she contracted rubeola and bronchopneumonia. This was followed in 3 wks. by a right suppurative otitis media accompanied by a tonsillitis, gingivitis and a furuncle of the right cheek. These incidents were attended by marked neutropenia and lymphocytosis, with recovery in each instance from the infection in approximately 1 wk., and from the neutropenia in about 8 to 14 days (Figs. 1 and 2). The patient was removed from the hospital after 6 wks.

Roentgenograms of the chest revealed an ill-defined stippling consistent with a bronchopneumonia. Prior to discharge, the long bones showed a ground glass appearance, slight thinning of the cortex, a corresponding widening of the medullary area, and several lines of arrested growth in the proximal and distal metaphyseal regions.

With the exception of the neutropenia and lymphocytosis, the differential blood counts were within normal limits. Hemoglobin, erythrocyte counts, bleeding, coagulation and prothrombin time, and reticulocyte counts were also normal.

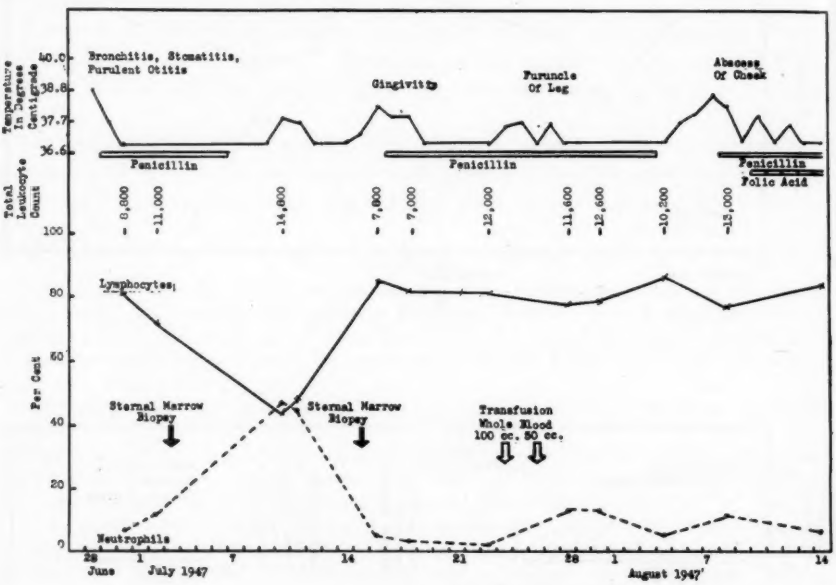

FIG. 3

Sulfadiazine by mouth and intramuscular penicillin did not appreciably alter her course except perhaps to control the acute infections.

The patient entered the hospital for the 3rd time at the age of 26 mos. with a history of fever and "swollen neck glands" of 3 to 4 days' duration. In the interim between these admissions she had been admitted to another hospital for a period of about 3 mos. where periodic neutropenia and lymphocytosis were also observed.

Although acutely ill and extremely irritable, she was well developed, well nourished, and weighed 13.6 kg. A right purulent otitis media, tonsillitis, abcess of the right cheek, and boggy and bleeding gums were present. Hyperpyrexia and moderate enlargement of the cervical lymph nodes were noted. Heart, lungs and abdomen were normal.

Her course was uneventful and she was discharged after 2 wks. of hospitalization.

Platelet count, reticulocyte count, bleeding, coagulation and clotting time, cerebrospinal fluid, and heterophile antibody were normal. Serology was negative. Blood vitamin C level, total protein, albumin, globulin, sugar, urea nitrogen and blood lead level were also within normal limits. Routine urinalysis was reported as negative.

Pentanucleotide and pyridoxine hydrochloride had no demonstrable effect.

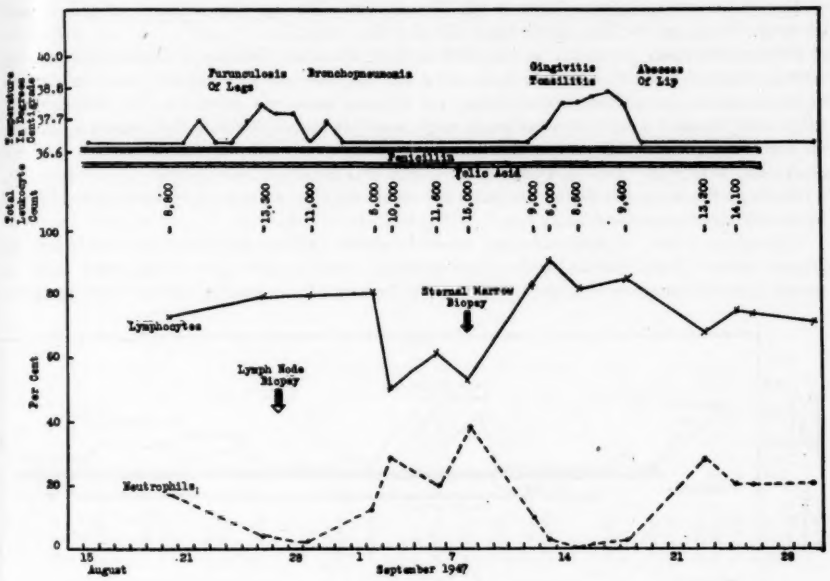
Temperature In Degrees Centigrade
40.0
38.8
37.7
36.6
Furunculosis Of Legs
Bronchopneumonia
Gingivitis Tonsillitis
Abscess Of Lip
Penicillin
Folic Acid
Total Leukocyte Count
- 8,800
- 13,300
- 11,000
- 8,000
- 10,000
- 11,600
- 15,000
- 9,000
- 6,000
- 8,800
- 9,400
- 13,200
- 14,100
100
80
60
40
20
0
Per Cent
Lymphocytes
Sternal Marrow Biopsy
Lymph Node Biopsy
Neutrophils
15
August
21
28
1
7
September 1947
14
21
28

FIG. 4

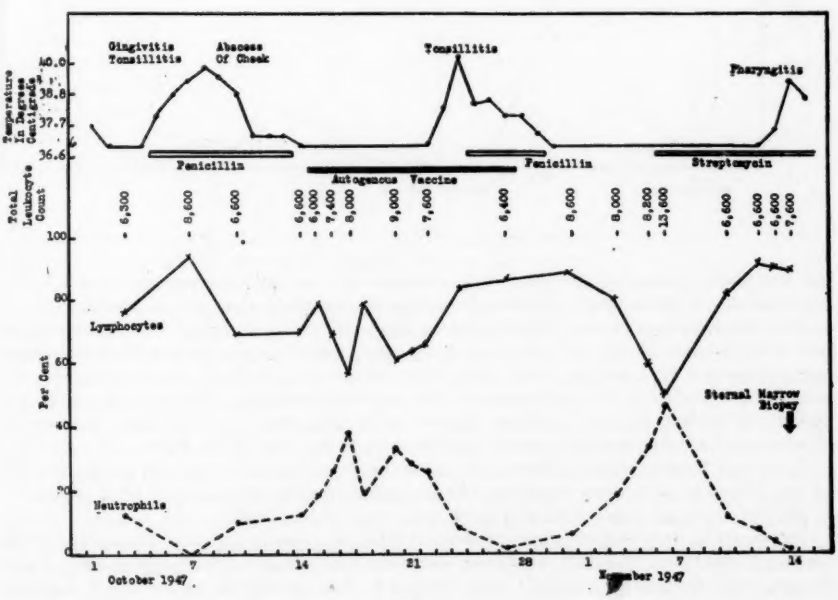
Temperature In Degrees Centigrade
40.0
38.8
37.7
36.6
Gingivitis Tonsillitis
Abscess Of Cheek
Tonsillitis
Pharyngitis
Penicillin
Autogenous Vaccine
Penicillin
Streptomycin
Total Leukocyte Count
- 6,300
- 8,600
- 6,600
- 6,600
- 6,000
- 7,400
- 8,000
- 9,000
- 7,600
- 6,400
- 8,600
- 8,000
- 8,200
- 13,600
- 6,600
- 6,600
- 6,600
- 7,600
100
80
60
40
20
0
Per Cent
Lymphocytes
Sternal Marrow Biopsy
Neutrophils
1
7
14
21
28
October 1947
1
7
14
November 1947

FIG. 5

Her 4th and last admission began 1 wk. after her last discharge with a history of cough, nasal discharge, fever, and swelling of the upper lip of 3 days' duration.

Examination again revealed a well developed, well nourished, listless and irritable patient with a temperature of 38.8° C. Upper lip was edematous and indurated with an ulcer 1 cm. in diameter on the mucosal surface. Hypertrophic, boggy and bleeding gums and infected tonsils were observed. Moderately enlarged, discrete cervical lymph nodes were palpated. Spleen and liver were not increased in size. Heart, lungs, skin and neurologic examination were within normal limits. Six per cent neutrophils were found in the peripheral smear shortly after she entered the hospital.

Although the leucocytes did not return to normal for 11 days, the patient appeared clinically well by the 3rd day of hospitalization.

Throughout 9 mos. of hospitalization, repeated episodes of fever and infection characterized her clinical course. These episodes of fever and infection lasted 5 to 7 days during which time the patient appeared restless, irritable and extremely drowsy. This contrasted sharply with her active

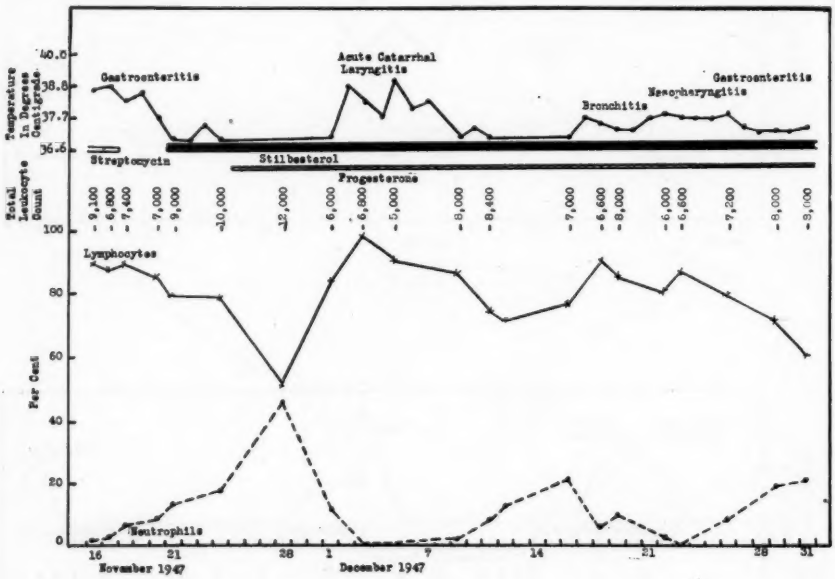

FIG. 6

and alert facies during her afebrile periods. Infections have included acute purulent otitis media, gingivitis, abscess of the cheek, tonsillitis, bronchopneumonia, furunculosis and gastroenteritis.

The hematologic course was characterized by rapid and usually complete disappearance of the neutrophils from the blood 1 to 3 days prior to the onset of the fever and infection. This neutropenia was accompanied by a marked relative and slight absolute lymphocytosis, slight monocytosis and leucopenia, and often by the appearance of a few atypical lymphocytes. The slow return to normal took 10 to 14 days, and was frequently initiated by the appearance of "stab" forms. These cycles of neutropenia and lymphocytosis recurred regularly every 18 to 23 days (Figs. 3 to 6).

In spite of these recurrent infections, the patient developed normally, weighing 15.4 kg. at 3 yrs. of age. Repeated examinations during the afebrile periods revealed only a shy and timid personality. She was discharged without alteration in the cyclic course of her disease.

Six sternal marrow biopsies were performed at different stages in the cycle. Fluctuations in the peripheral blood were essentially a reflection of the marrow cytology as manifested by the continual changes in the lymphoid and myeloid series (Table I.). Although the 4th marrow sample suggested leukemia with 6% blast forms, the others were not typical of this condition. The last marrow sample

had a relatively normal lymphoid and myeloid series, and strongly weighed against the diagnosis of leukemia.

Hemoglobin varied between 10.5 and 12.0 gm./100 cc. blood, and the erythrocyte count averaged about 4 million. Eosinophilia was noted on a few occasions varying between 5 and 8%. Neither lymphoblasts nor myeloblasts were found in the peripheral smears. Normal platelet counts, reticulocyte counts, clotting, bleeding and coagulation times, and hematocrit were reported.

Biopsy of a cervical lymph node revealed reticuloendothelial hyperplasia, but no immature cells of the lymphoid series.

Periodic blood sedimentation rates were performed. They were extremely rapid during the height of the neutropenic period, and slightly to moderately fast during the decline and recovery phases.

A positive tuberculin patch test was obtained.

Chest roentgenograms revealed normal lung fields and normal cardiac silhouette. Development of the carpal and tarsal bones was consistent with her chronologic age just prior to her discharge.

TABLE I

STERNAL MARROW BIOPSY FINDINGS

	July 3, 1947	July 15, 1947	Sept. 8, 1947	Nov. 14, 1947	Jan. 19, 1948	Mar. 12, 1948
Blasts	0.4	1.4	0.1	6.8	0.8	4.4
Myelocytes neutrophilic	12.2	4.2	1.3	7.0	2.6	2.2
Myelocytes eosinophilic	4.4	3.8	5.0	0.2	2.6	4.0
Metamyelocytes neutrophilic	3.0	1.4	1.0	8.8	0.6	4.0
Metamyelocytes eosinophilic	0.0	0.0	1.0	0.4	0.0	1.4
Non-segmented neutrophiles	8.6	1.2	11.8	11.8	7.8	26.4
Non-segmented eosinophiles	2.8	1.8	3.8	1.2	2.0	0.6
Segmented neutrophiles	8.0	0.0	4.6	14.8	4.8	7.8
Segmented eosinophiles	5.8	3.0	2.3	1.2	2.0	1.2
Lymphocytes	49.4	78.8	38.3	38.4	64.4	27.8
Monocytes	2.2	1.2	0.3	2.4	2.8	0.6
Plasma cells	0.2	0.6	0.5	0.6	1.0	1.2
Unclassified cells	1.6	1.0	0.5		1.6	0.4
Megakarocytes	1.2	0.4	0.6	0.6	0.4	0.2
Megaloblasts	3.0	2.5	2.1	0.2	0.0	1.0
Erythroblasts	3.0	3.5	2.1	2.4	0.2	0.8
Pronormoblasts	9.0	10.5	7.6			
Normoblasts	20.0	21.0	17.6	12.0	6.8	15.8

Lines of arrested growth with definite widening of the medullary cavity and thinning of the cortex persisted in the long bones. Skull roentgenograms were normal.

The following blood estimations were within normal limits: uric acid, urea nitrogen, sugar, calcium, phosphorus, alkaline phosphatase, creatinine, and cholesterol and esters. The Paul-Bunnel test was repeatedly reported negative. Wassermann test was negative, and agglutinations for typhoid, paratyphoid A and B, Proteus X19, and brucellosis were negative in all dilutions.

Giardia lamblia was found in the stools, but subsequent examinations for ova, parasites and pathogenic bacteria were negative.

Penicillin intramuscularly, 50,000 units every 3 hrs., was given continuously for over 6 wks., and parenteral streptomycin, 1.5 gm. daily, for almost 2 wks. Neither altered the episodes of agranulocytosis and lymphocytosis; they probably controlled the more severe concomitant infections.

An autogenous vaccine was made from the infected tonsils and abscessed cheek. The initial dose of 50 million organisms subcutaneously was increased daily until 5 billion were given by the end of 2 wks. Folic acid 5 mg. was also given daily for 1 mo. Neither the folic acid nor vaccine had any noticeable effect.

The patient received 2 transfusions of whole blood of 100 ml. and 50 ml., respectively. She was also given daily doses of stillbesterol 5 mg. and progesterone 20 mg. for 6 wks. The latter

treatment resulted in increased pigmentation of the breast areolar and hypertrophy of the vaginal labia and mucosa. Both estrin therapy and transfusion with whole blood seemed to suppress the neutrophils.

Estrin, prolan and 17-ketosteroid determinations were performed on urinary samples obtained at various stages in the disease. The patient was followed in the outpatient department where her parents were somewhat more successful in securing sufficient 24 hr. specimens of urine.

On two occasions biologic assay on 500 ml. of urine revealed 4.5 and 9.5 international rat u. of estrin just prior to the onset of the neutropenia and lymphocytosis. Shortly after the neutrophils began to disappear only a trace of estrin was found. Five determinations during various other periods in the cycle failed to reveal even a trace of estrin.

When the estrin was elevated, one test for prolan was positive. Four other determinations were negative.

Two estimations of the 17-ketosteroid were within normal limits.

Discussion

Cyclic neutropenia seems to have a distinct clinical and hematologic pattern that separates it from other types of agranulocytosis. The characteristic of this pattern is the cyclic regularity with which the attacks occur every three weeks. Usually the disease lasts for many years, but the patient may succumb early to one of the acute infections which accompany each period of neutropenia. Although case reports of three or four attacks of recurrent granulocytopenia are not unusual in the medical literature, they do not typify this illness. These cases probably have a different etiology or perhaps represent mild or atypical forms. The patient must be observed over a long period of time before the diagnosis can be established.

It appears fairly certain that in a large percentage of cases of cyclic neutropenia, the primary disturbance takes place in the bone marrow, and that cessation of the myeloid growth precedes, rather than follows, other evidence of the disease. Careful observation and almost daily blood counts for a period of months reveals this to be true in this patient, where the drop in neutrophils precedes the fever, infection and stomatitis by two or three days. Repeated marrow biopsies have shown that the disappearance of the neutrophils is due to the primary suppression of the myeloid elements in the marrow and not due to the phagocytic action of the spleen or other organ. An increase in "blast" forms in the fourth marrow aspiration led at one time to a presumptive diagnosis of leukemia; however, further marrow studies, blood chemistries, clinical course and lymph node biopsy have ruled against the latter diagnosis.

Twelve months of direct observation of the patient on the hospital ward during a two year period have made possible the exclusion of most of the well known etiologic agents of agranulocytic angina. No common denominator in the diet, drugs or contacts was apparent during this time. Although sulfadiazine was first suspected, it has been eliminated for all practical purposes as the etiologic agent; the patient has not received sulfonamide in any form for the past two years.

The three week cycles have suggested to several authors a possible causal relationship between menstruation and the fluctuations in the neutrophils.[2,4,5,9] Empirically, the patient was given stilbesterol and progesterone, and the neutrophils apparently were suppressed during the time the medication was given (Fig. 6) and for several weeks after it was discontinued. In retrospect, it was also realized that two small whole blood transfusions apparently had suppressed the neutrophils for six weeks (Fig. 3). Unfortunately, detailed information on the donor could not be obtained. This suppression and the output of estrin on two occasions just prior to an attack was highly suggestive of a female sex hormone imbalance. The etiology might be a combination of female endocrine disturbance

and a constitutional susceptibility of the neutrophils to estrin. Such a combination of factors would account for the rarity of this disease in infants and males.

In three of the reported cases in adult women, the authors found that menstruation preceded the attacks by three to seven days.[2,4,5] Thompson[9] studied an adult male with cyclic neutropenia, and found a fluctuating female sex hormone excretion which closely followed the daily number of neutrophils in the peripheral blood. In the case reported by Stephens and Lawrence,[5] the cycles were related to menstruation, but they could find no correlation between estrin excretion and the white blood cell level; however, bilateral oopherectomy resulted in a cessation of the cycles one year after operation. On the other hand, Doan[3] observed a case for one year in a young adult female and could find no relationship between the periodic attacks and the menstrual cycle. With the exception of the latter case, the findings of these authors tend to confirm those in this case.

It was felt that antibiotic therapy probably prevented the present case from terminating fatally on several occasions, but this actually was palliative therapy and did not affect the progress of the disease. None of the tested therapeutic measures prevented the recurrent attacks. In a patient nearing menopause, bilateral salpingo-oopherectomy resulted in an apparent cure.[5] However, such an operation was considered too radical therapy in this particular case.

Summary

A case of cyclic neutropenia of over 2½ years' duration is reported in a female infant. The cyclic fluctuations of the clinical and hematologic picture over a long period of time is emphasized. A casual relationship between female sex hormone and cyclic neutropenia is suggested by estrin therapy and excretion.

Acknowledgment

Acknowledgment is made to Dr. Charles H. Birnberg, Dr. Daniel A. Sherber and Dr. Annie Laufer of the Jewish Hospital of Brooklyn Endocrine Laboratory for their hormone excretion studies.

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Spanish Abstract

Neutropenia Cíclica en un Infante

Repetidos episodios de neutropenia, linfocitosis, infección y fiebre fueron observados en un infante desde la edad de 5 meses hasta 2½ años. Los ciclos reaparecian cada tres semanas y principiaban con el rápido y generalmente completo desaparecimiento del neutrófilo; esta neutropenia venía

acompañada por una ligera monocitosis y leucopenia, un aumento relativamente marcado y algo absoluto en linfocitos, y la aparición de unas cuantas formas atípicas de las últimas células. Dos o tres días más tarde el paciente generalmente desarrollaba una infección aguda, fiebre y lasitud. El restablecimiento clínico tuvo lugar en una semana, y el restablecimiento hematológico en dos semanas. El exámen físico durante sus períodos asintomáticos fué esencialmente negativo.

Un aumento en estrógenos urinarios y un prolán positivo antes de la neutropenia sugerieron una relación entre un desorden de endocrina femenina y los ciclos hematológicos. Seis biopsias de médula esternal mostraron un variante patrón de leucocitos; pero dejó de establecer una diagnosis de leucemia. Los ensayos de laboratorio fueron normales. Los roentgenogramas revelaron una apariencia de vidrio molido de los huesos largos y un ensachamiento de la cavidad medular; pero un desarrollo carpal y tarsal normal.

La terapia stilbestrol y progesterona y una transfusión de sangre entera aparentemente suprimió el neutrófilo. La sulfadiazina, penicilina y estreptomicina ayudaron a controlar las infecciones, pero no alteraron su curso. La terapia de vacuna autógena, ácido fólico, pentonucleotida, piridoxina HCL no mostraron ningún efecto.

32 East Mineola Avenue

STUDIES OF PENICILLIN IN PEDIATRICS

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(*with the technical assistance of* H. MACLEAN, A.B.)
Chicago, Ill.

THEORETICALLY, the concentration of penicillin in blood for therapeutic purposes should be at least equivalent to, or greater than, the minimum concentration by which the specific infecting organism is inhibited.[1] Also, theoretically, this level should be maintained until the bacteria are killed or the patient is beyond doubt of recovery. This study was planned, therefore, to determine the concentration of penicillin by which various infecting bacteria are inhibited and to test some of the available methods for maintaining that concentration in the serum of the patient.

A study was made of data on the relative degrees of sensitivity to penicillin (i.e., the minimum concentration of penicillin required to inhibit growth) of various organisms encountered in human infections. Based upon these data, an investigation was conducted to determine the dosage of penicillin in relation to weight and various methods of its administration for attaining and maintaining these concentrations of penicillin in the serum of infants and children.

SENSITIVITY TO PENICILLIN OF VARIOUS BACTERIA ENCOUNTERED IN INFECTIONS OF INFANTS AND CHILDREN

The ranges of sensitivity to penicillin of various pathogenic bacteria have been studied by several investigators,[2-7] all of whom except Bodian isolated them from adults. Their results are given in Table I.

The 68 bacterial strains in our study were isolated by culture from infected areas, exudates or fluids of sick infants and children in the hospital. The results are shown graphically in Chart I and listed in Table I.

The method used for determining the degree of sensitivity of a bacterial organism to penicillin was a serial dilution technic.[7]

The data show that the mean concentration of penicillin to which β Str. hemolyticus was susceptible was 0.17 u./cc., and the mean concentration for α Str. hemolyticus was 2.5 u./cc. These figures are higher than those of other investigators. Some of our data, however, were collected from tests of bacteria isolated from patients who had not responded satisfactorily to penicillin and who were subsequently hospitalized. Meads et al.[4] and Hamilton et al.,[5] on the other hand, reported the sensitivity to penicillin of bacteria which had not been exposed to penicillin prior to testing, and their results, therefore, reflect the sensitivity of such a population of bacteria. Our data show the possibilities under different conditions for encountering pathogenic organisms which are resistant to concentrations beyond those they reported.

From the Kunstadter Laboratories for Pediatric Research and the Department of Bacteriology, Medical Research Institute and Sarah Morris Hospital for Children of Michael Reese Hospital. This study was supported in part by the Michael Reese Research Foundation.

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TABLE I

MINIMUM CONCENTRATION OF PENICILLIN IN OXFORD u./ML. REQUIRED TO INHIBIT VARIOUS PATHOGENIC BACTERIA

		Staph. aureus Hemolyticus	β Str. Hemolyticus	α Str. Hemolyticus	H. Influenzae	Meningococcus	D. Pneumoniae
Spink et al.[3] 1944	no.	67					
	min.	0.05	—	—	—	—	—
	max.	0.8					
	mean[a]	0.19					
Bondi et al.[3] 1945	no.	115					
	min.	0.05	—	—	—	—	—
	max.	>4.05					
	mean[a]	>0.45					
Meads et al.[4] 1945	no.	36[b]	14	24	21[e]	54	88
	min.	0.016	0.004	0.008	0.031	0.016	0.008
	max.	2.0	0.016	0.125	0.5	0.5	0.063
	mean[a]	0.33	0.008	0.03	0.10	0.08	0.021
Hamilton et al.[5] 1946	no.	86[c]	33	42[d]			10
	min.	0.01	0.0012	0.0025	—	—	0.0025
	max.	2.85	0.17	5.71			0.04
	mean[a]	0.35	0.017	0.048			
Bodian et al.[6] 1946	no.	86	20			1	8
		86% of 123 strains (includes 1 C. diphtheriae and 7 Staph. albus) inhibited by 0.1 u./ml. or less					
Fleming et al.[7] 1946	no.	557	128	77	1		4
	min.				100	—	
		48% sensitive to 1.0 or less	90% sensitive to 1.0 or less	94% sensitive to 1.0 or less			100% sensitive to 0.5 or less
Present study	no.	27	10	26	2[f]	1	2[g]
	min.	0.04	0.08	0.04	0.31	1.25	0.04
	max.	5.0	5.0	10.0	1.25		0.62
	mean	0.36	0.17	2.5			

[a] Calculated from author's data.
[b] Includes 9 Staph. nonhemolyticus.
[c] Staphylococci, types not differentiated.
[d] Includes Str. nonhemolyticus.
[e] Respiratory strains.
[f] Type b, from cerebrospinal fluid.
[g] Types 5 and 29.

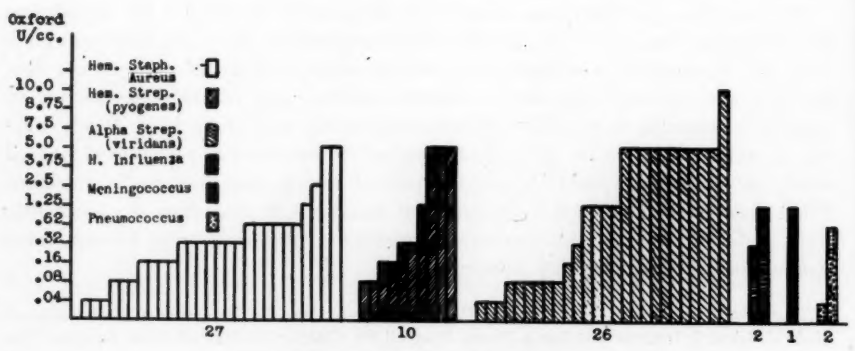

CHART I. Minimum concentration of penicillin which inhibits various bacteria isolated from sick infants and children

Different strains of bacterial pathogens vary considerably in their sensitivity to penicillin. The expression "minimum effective blood level of penicillin" is obviously misleading when it refers to a routine test organism rather than to the specific infecting bacterium. The lowest concentration of penicillin which inhibits the specific infecting organism *in vitro* may be considered to be a minimum effective serum concentration for that particular organism. An optimum serum penicillin concentration may be 2 to 10 times that, depending upon many other factors, such as location of the infection, the relation of the serum concentration to the concentration at the site of the infection and the number of infecting bacteria. (There is some evidence, based on *in vitro* studies, that concentrations of penicillin above an "optimum" may be less actively bactericidal than are "optimum" concentrations of the drug.[8])

Although most α and β Str. hemolyticus not previously exposed to penicillin may be sensitive to 0.04 u./ml., most Staph. hemolyticus under the same conditions are resistant to concentrations of less than 0.4 u./ml., or 10 times that amount. Some strains of a susceptible group of bacteria, such as the β Str. hemolyticus, particularly if previously exposed to sublethal concentrations of penicillin, were found to be resistant to concentrations of less than 5.0 u./ml.; on the other hand, one strain of H. influenzae, which as a group is generally considered to be relatively resistant, was relatively sensitive. Most pneumococci have been found to be sensitive to less than 0.04 u./ml. The mean sensitivity for meningococci was 0.08 u./ml., but one strain was found which was resistant to concentrations less than 1.25 u./ml.

Concentrations of Penicillin in Serum in Relation to Varying Dosages and Methods of Administration

The second part of this study was directed to determining the concentrations of penicillin obtained in serum following various dosages and methods of administration.

Although numerous investigators have studied the clinical response to penicillin of infants and children, relatively few have reported studies on dosage and the concentrations of penicillin in the serum. Florey,[9] working with adults in 1944, recommended a dosage of 125 u./lb. body weight of penicillin in saline to be given intramuscularly every three hours. Bodian,[6] in 1946, reported that in 61 infants under one year of age administration of 166 u./lb. body weight resulted in a serum penicillin concentration of 0.02 u./ml. in 82% of cases at the end of three hours and in 67% at the end of four hours. Later that year Buchanan[10] stated that this dose was often inadequate. He showed, on the basis of experimental work with six cases, that 250 u./lb. every three hours was more satisfactory. With this dosage he found an average of 0.03 u./ml. at the end of 2½ hours, as read from Figure 1 in his report. However, for a greater margin of safety he recommended that 500 u./lb. be given every three hours intramuscularly. With this dosage he found serum concentrations after 2½ hours of 0.06-0.125 u./ml., as read from Figure 2 of his report. On the other hand, Cooke and Goldring[11] in this country reported in 1945 that they found no close relationship between penicillin concentrations in the blood and the number of units of penicillin in saline given intramuscularly per kilogram body weight, although the highest levels were found in those patients receiving relatively large doses. Their report gives data on serum penicillin concentrations following doses of 375 to 2,800 u./kg. given to nine children under 16 years of age. They state that there may have been some irregularities in timing the administration of the dosages because of reduced wartime personnel.

Because of these differences and because of the meager amount of information on this problem in the literature, one of the aims of the second portion of this study was to investigate the concentrations of penicillin in the serum following intramuscular administration of varying dosages of crystalline sodium penicillin G in saline. Other vehicles were also studied, such as sesame oil (Emulgen)* and beeswax and peanut oil (new Romansky type formula).† Crystalline sodium salt of penicillin G was used in all these preparations except the last where the potassium salt was used. In addition, some data were obtained on the rectal administration of crystalline sodium penicillin G suspended in cocoa-butter‡ and also of this same form placed in gelatin capsules.

While this study was in progress, several related reports were published. Hoffman,

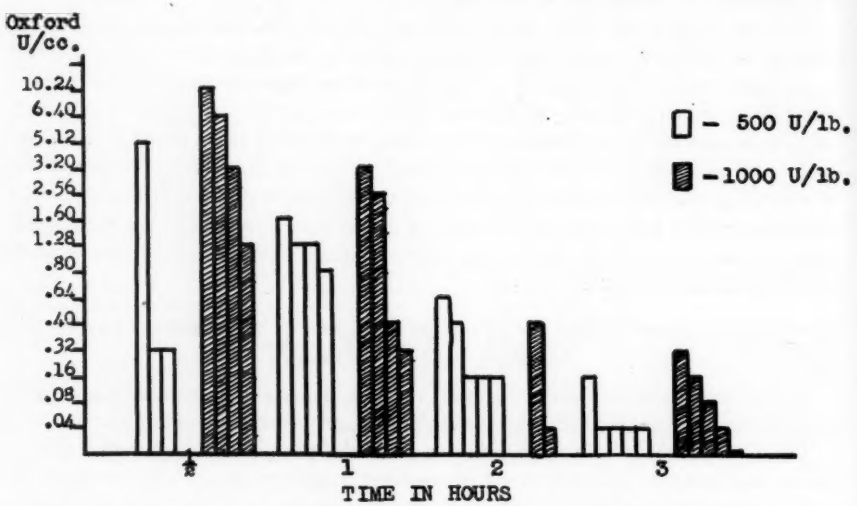

CHART II. Penicillin serum levels following administration in saline intramuscularly

Hofer and Gordon[12] reported on the concentrations of penicillin obtained in serum with orally administered solutions, Mandel and Thayer[13] on the concentrations obtained following rectal administration, and Riley and Strong[14] and Adams and Fisher[15] on concentrations obtained following administration of penicillin in the earlier form of peanut oil and beeswax (original Romansky formula).[16]

In this project the serum penicillin concentrations in 48 infants and children were studied. The ages ranged from 5 weeks to 12 years (average 4 years). Their weights ranged from 3.6 to 50 kg. (average 13.6 kg.). All patients were kept at complete bed rest during the studies.

The doses were measured and given with more than usual care, and blood specimens were withdrawn at carefully timed intervals. The concentrations of penicillin in the serum were checked by two workers independently (L. K. and H. M.). They were determined by a modification of the Kolmer serial dilution technique[17] using a standard

* Supplied by Dr. H. L. Daiell, Lakeside Laboratories, Milwaukee, Wis.

† Supplied by Commercial Solvents Corporation, New York, N.Y.

‡ Prepared by Dr. E. Mandel, U. S. Public Service, Marine Hospital, Chicago, Ill.

Staph. aureus strain 209 P.* This organism is sensitive to 0.04 u./ml. of penicillin. Frequent checks showed that its sensitivity did not change throughout the course of this study.

Ten patients were given a single dose of penicillin in saline intramuscularly; 5 were given 500 u./lb.; and 5 were given 1,000 u./lb. Blood was drawn at ½, 1, 2, and 3 hour intervals (Chart II).

Of the 5 patients given 500 u./lb., all had 0.04 u./ml. or more at the end of 3 hours. Of the 5 patients given 1,000 u./lb., 1 had no demonstrable penicillin in the blood at the end of 3 hours; the remaining 4 had 0.04 u./ml. or more. The highest concentration attained at the end of 3 hours was 0.16 u./ml. with 500 u./lb. and 0.32 u./ml. with 1,000

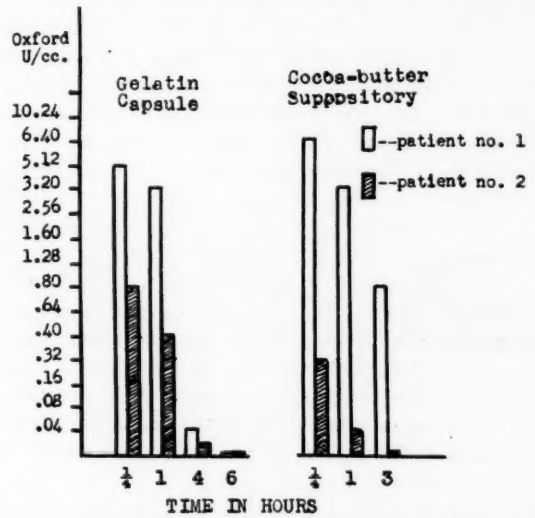

CHART III. Penicillin serum levels following rectal administration

u./lb. The average concentration at the end of 3 hours was 0.06 u./ml. with 500 u./lb., and the average with 1,000 u./lb. was approximately double this (0.14 u./ml.). Nevertheless, it is clear (Chart II) that penicillin in saline given intramuscularly in either dosage gave considerable variations in serum penicillin concentrations at the end of three hours. Because these variations under well controlled conditions were similar to those noted by Cooke and Goldring,[11] further extensive studies along this line were not done.

Recently, Mandel and Thayer[13] showed that good serum concentrations were attained in adult patients when this antibiotic was given rectally. This was apparently true in spite of the evidence that penicillinase produced by bacteria in the rectum might destroy the penicillin. If penicillin could be given rectally, this route might be useful particularly in infants and children in preference to intramuscular injections.

Each of four patients was given crystalline sodium penicillin G 10,000 u./lb. as a single dose per rectum (Chart III). Two received the dose in cocoa-butter and beeswax suppositories and two in gelatin capsules. The first patient who was given a cocoa-butter suppository showed a level of 6.4 u./ml. at 15 min., 3.2 u./ml. at 1 hr., and 1.28 u./ml.

* Supplied by the Federal Security Agency, Food and Drug Administration, Washington, D.C.

at 3 hrs. The other case, in which there was some leakage, showed a level of 0.32 u./ml. at 15 min. and 0.04 u./ml. at 1 hr. No level was assayable at three hours. One patient given a gelatin capsule suppository containing penicillin 10,000 u./lb. showed a level of 5.12 u./ml. at 15 min., 3.2 u./ml. at 1 hr., and 0.04 u./ml. at 4 hrs. The other patient given a gelatin capsule suppository showed a level of 0.8 u./ml. at 15 min., 0.4 u./ml. at 1 hr., and no demonstrable penicillin at 4 hrs. From these few cases it is apparent that 10,000 u./lb. given rectally in the manner stated cannot be depended upon to maintain a serum concentration of 0.04 u./ml. for 4 hrs. Further work may show that 10,000 u./lb. given rectally every three hours may, in special cases, be a satisfactory alternative to giving 1,000 u./lb. intramuscularly in saline every three hours when other routes are contraindicated. In addition to the large dose, rectal administration is disadvantageous because it requires an individual to stay with the child for at least 15 minutes after inserting the suppository in order to avoid leakage. The interesting finding in this part of the study is the high serum concentrations of penicillin within 15 minutes after the suppository was given. This confirms the finding of Mandel and Thayer.[13]

In order to prolong the duration of an adequate serum concentration of penicillin when given intramuscularly, sesame oil was tried as a suspending agent which might delay the absorption of the penicillin. Crystalline sodium salt of penicillin G was therefore suspended in sesame oil emulsion (Emulgen) and given to six cases. The suspension was prepared by dissolving penicillin 200,000 u. in 0.5 ml. of normal saline and mixing the latter with 1.5 ml. of sesame oil. A dose of 3,000 u./lb. was given to each of two patients. At the end of 8 hours, one patient had a serum concentration of 0.04 u./ml. and the other had no demonstrable penicillin. Two patients were each given 5,000 u./lb. After six hours a level of 0.04 u./ml. was found in one patient, and none was found in the other. Ten thousand units per pound were given in each of two additional cases. With this dosage, 0.16 u./ml. and 0.08 u./ml. were found at the end of six hours. At 10 hours, one of these patients had 0.04 u./ml. and the other had none. No intolerance to sesame oil emulsion was noted in these six patients.

Thus, 10,000 u./lb. were required to obtain a level of 0.08 u./ml. at the end of six hours. Harris et al.[18] reported that the serum penicillin concentrations produced by the use of sesame oil suspensions were inconstant. Both because of the high dosage required to attain significant blood levels and because of the inconstant results, further work with crystalline sodium penicillin G in sesame oil emulsion was not done.

Penicillin in peanut oil and beeswax (the new type Romansky formula,[19] which is fluid at room temperature) was given to each of 31 patients. This preparation has the advantage over the old one[16] in that no heating is required. Each cubic centimeter contained potassium penicillin G 300,000 u. It is necessary to shake the ampules vigorously before withdrawing the desired amount to assure a homogeneous suspension. A dry sterile 2 cc. syringe and a dry 20 gauge needle were found to be satisfactory for administration. In all cases the buttocks were used as the site of injection.

Four thousand units of penicillin in this preparation per pound body weight were given intramuscularly to each of 31 patients (Chart IV). Concentrations of 1.28 to 5.12 u./ml. were found ½ to 1 hour after the injection. The concentrations then fell gradually over more than a 24 hour period. The average serum penicillin concentration at the end of 24 hours was 0.18 u./ml. The serum of 29 of the 31 patients showed 0.04 u./ml. or more of penicillin at the end of 24 hours (94% of the patients).

Adams and Fisher[15] gave crystalline sodium penicillin 5,000 u./lb. in the older

Romansky preparation, reporting that 82% showed serum concentrations of 0.03 u./ml. or higher in the period 22 to 24 hours after injection. They point out, however, that the majority of their patients were ambulatory and that the rate of absorption is "significantly greater with muscular activity." All the patients in this study were kept in bed constantly throughout the test periods.

With a dose of 4,000 u./lb. of this newer preparation, serum concentrations of 0.32 to 1.6 u./ml. (average 0.60 u./ml.) were obtained at the end of 12 hours. Therefore, in infections due to organisms sensitive only to this higher concentration of penicillin, 4,000 u./lb. given every 12 hours would give the desired serum concentrations over a prolonged period. This dosage and frequency have been found to be particularly helpful

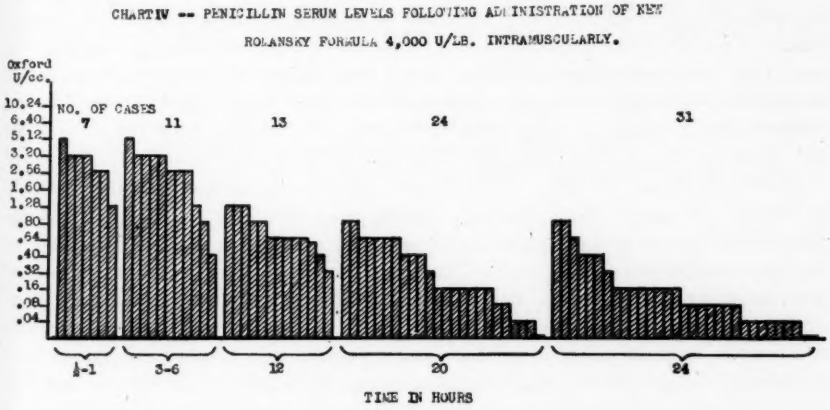

CHART IV

in stubborn infections due to the more resistant strains of Staph. aureus hemolyticus (see earlier part of this study). It was especially apparent in two cases of osteomyelitis in infants who improved significantly only after receiving this dosage at this decreased interval.

All the patients were followed for at least two weeks after receiving their last injection of this preparation. None had significant untoward reactions except that small indurated nodules were occasionally noted at the injection site in patients receiving numerous repeated doses. These disappeared without treatment within six days. The most marked example of this was seen in a Negro boy, 4 years of age, who received four 1.0 ml. doses of 300,000 u./ml. (32,000 u./lb.) once daily for five days. The nodules in this case disappeared within six days.

DISCUSSION

Pathogenic bacteria vary considerably in their degree of sensitivity to penicillin. Most strains of β Str. hemolyticus and approximately half of the strains of α Str. hemolyticus not previously exposed to penicillin are inhibited by penicillin 0.04 u./ml. On the other hand, a concentration of 10 times this amount, or 0.4 u./ml., is required to inhibit the growth of most strains of Staph. aureus hemolyticus under the same condition.

Some strains of organisms, such as β Str. hemolyticus, that belong to a group of which most strains are sensitive to less than 0.04 u./ml. may be resistant to concentrations up

to 5.0 u./ml., particularly if previously exposed to sublethal concentrations of penicillin. On the other hand, one strain of H. influenzae was found to be sensitive to 0.31 u./ml. although it belongs to a group of which most strains are relatively resistant to penicillin. The concentrations of penicillin to which most of the strains of α and β Str. hemolyticus were sensitive were higher than those reported by other investigators. This may have been due to the fact that a number of our cultures were taken from patients who had been receiving penicillin prior to admission to the hospital. Such higher resistance may have been due to the persistence of resistant cells from a penicillin-sensitive strain which, in the presence of lower concentrations of penicillin, multiplied rapidly and thus established a uniformly more resistant strain.[20]

It is not practical to refer to an arbitrary effective minimum or adequate serum penicillin concentration for all cases. It is preferable to consider as a minimum effective concentration of penicillin that concentration which inhibits the specific infecting organism isolated from the particular case. Ideally, in seriously ill infected children, the organism should be isolated and tested for sensitivity. When this is not practical, it is well to aim at serum concentrations of no less than 0.04 u./ml. in the average streptococcal infection and of no less than 0.4 u./ml. in the average staphylococcal infection.

To attain such concentrations various routes, excipients and dosages were tried. Sodium penicillin G in saline 500 u./lb. body weight given intramuscularly gave an average serum concentration of 0.06 u./ml. at the end of three hours, and 1,000 u./lb. gave an average concentration of 0.14 u./ml. The range, however, was considerable, and out of five patients given 1,000 u./lb., one had no demonstrable serum penicillin at the end of three hours. Even doses as high as 10,000 u./lb. of sodium penicillin G in cocoa-butter and beeswax suppositories or in gelatin capsules given rectally cannot be depended upon to maintain a demonstrable serum concentration for four hours. It is of interest that high serum penicillin concentrations were obtained within 15 minutes after administration of the drug by this route.

When sesame oil was used as the excipient for penicillin, 10,000 u./lb. were required to obtain a concentration of 0.08 u./ml. six hours after intramuscular administration.

A dose of 4,000 u./lb. of penicillin in the new type Romansky formula[19] (peanut oil and beeswax, fluid at room temperature) was found to maintain a serum penicillin concentration of 0.04 u./ml. or more for 24 hours in 94% of the cases. This concentration is equivalent to or greater than that required to inhibit the growth of most strains of the following organisms: α and β Str. hemolyticus and D. pneumoniae (Table I). At 12 hours, this dosage maintained a serum concentration of 0.32 u./ml. or higher. The average concentration maintained by this dosage and interval (0.60 u./ml.) is greater than the minimum inhibiting concentration for most strains of Staph. aureus hemolyticus and of meningococcus.

Summary

A study is made of the relative degrees of *in vitro* sensitivity to penicillin of various pathogenic bacteria. Different strains vary considerably in their sensitivity to penicillin. The concentrations of penicillin obtained in the serum following varying dosages per unit body weight in infants and children when given in the following forms are reported: crystalline sodium penicillin G in saline given intramuscularly; the same compound of penicillin in gelatin capsules and in cocoa-butter and beeswax suppositories given rectally; crystalline sodium penicillin G in sesame oil given intramuscularly, and crystalline potas-

sium penicillin G in a new type Romansky formula given intramuscularly. The last preparation, when given in doses of 4,000 u./lb., maintained serum penicillin concentrations 24 hours after administration in 94% of cases, which was above the minimum concentration required to inhibit most strains of α and β Str. hemolyticus and of M. pneumoniae, and the serum concentrations obtained with this preparation 12 hours after administration were equal to or above the minimum concentration required to inhibit most strains of Staph. aureus hemolyticus and of meningococcus.

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SPANISH ABSTRACT

Estudios de Penicilina en Pediatria

Se hace un estudio de los grados relativos de la sensibilidad *in vitro* a la penicilina de varias bacterias patogénicas. Las diferentes cepas varian considerablemente en su sensibilidad a la penicilina. Las concentraciones de penicilina obtenidas en el suero después de dosis variantes por unidad de peso de cuerpo en infantes y niños cuando se dan en la siguientes formas son: penicilina G de sodio cristalino en salina administrada intramuscularmente; el mismo compuesto de penicilina en cápsulas de gelatina y en supositorios de manteca de cacao y cera de abejas administradas por el recto;

penicilina G de sodio cristalina en aceite de sésamo administrada intramuscularmente, y penicilina G de potasio cristalina en un nuevo tipo de fórmula Romansky administrada intramuscularmente. La última preparación cuando se dió en dosis de 4,000 u./lb. mantuvo las concentraciones de penicilina de suero, 24 horas después de la administración en 94% de casos, que fueron superiores al mínimo de concentración requerido para inhibir la mayor parte de las cepas de hemoliticus A y B y de penumoniae M, y las concentraciones de suero obtenidas con esta preparación 12 horas después de la administración fueron iguales o superiores al mínimo de concentración necesario para inhibir la mayor parte de las cepas de Staph. aureus hemolyticus y de meningococcus.

29th and Ellis Avenue

CHRONIC RESISTANCE TO SLEEP IN INFANCY

By BENJAMIN SPOCK, M.D.
Rochester, Minn.

TWENTIETH century America has no stable tradition about how children should be reared. In fact, it has a tradition against traditions. Parents in a quandary do not ask themselves what their own parents or grandparents would have done under the circumstances. They ask what is the latest theory. Twenty years ago, strictness and regulation were the psychologic and pediatric laws of the land. Now we are in the midst of a strong, even violent, swing in the opposite direction. The first impetus came from psychiatrists and educators who had observed the unfortunate effects on at least some individuals, both children and parents, of extreme rigidity in upbringing. Pediatricians began to experiment with new approaches. The so-called self-demand method of feeding, which seemed anarchistic when it was first reported only a few years ago,[1] is now becoming the normal procedure in various parts of the country. There is a tendency to postpone weaning and toilet training and to inaugurate them with regard for the baby's readiness. It no longer takes courage for a physician or psychologist to advocate cuddling.

We seem to be moving in the right direction; a more friendly attitude toward babies, a more natural, relaxed regimen for their care, a respect for their individual needs and developmental levels is good for both them and their parents. But this swift transition is not without its difficulties. The same unstable responsiveness to a new theory, which 25 years ago made some people so enthusiastic for regulation, is today making the corresponding minority totally and uncritically devoted to self-regulation and self-expression. This is creating a certain number of problems and a certain number of unhappy children. But there is another risk, too. If we cannot as physicians control the swing and prevent foolish extremes, the philosophy of friendliness and flexibility may in its turn become discredited and lead to a new phase of severity.

Children are parasitic on their parents for their physical and emotional needs. Among the latter are not only love, understanding and freedom from unreasonable domination, but also the security that comes from parents whose actions show that they know perfectly well what is sensible and what is not and who have no hesitation in communicating it. The good parent must use his or her good judgment, decisiveness and leadership a hundred times a day in steering, stopping and starting the average small child. The child not only gets into trouble without control, he is miserable without it.

Chronic resistance to sleep in infancy is a behavior problem which was formerly rare but is now becoming more frequent. Its frequency seems related to the trend toward self-regulation and greater kindliness to babies and to confusion in how to apply this philosophy. An extreme case is that of an infant brought to the physician at 9 months of age

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who refuses to be put down to sleep in the evening and who insists on being carried about for a good part of the day. His mother states that though he is drooping with fatigue at 7 p.m. he screams angrily when she tries to lay him in his crib. She carries him around for another half hour and then tries again. He will give in about 10 p.m. if she lays him on her own bed and lies down beside him. When she and her husband go to bed they transfer him gingerly to his crib, but he may waken then or an hour later and cry furiously until picked up. Then the walking begins all over again.

The mother describes him as half falling asleep in her arms. His eyes close and his head falls forward, but he immediately arouses himself with a grim look, as if he were declaring: "I mustn't let myself give in." In the early weeks of this nightly struggle the baby is said to have given up after half an hour. But as time has passed he has learned to keep himself awake longer and longer. Now he is able to keep his mother walking up to three hours. He doesn't sleep late in the morning either, though he tends to lengthen his midmorning and afternoon naps. This is not sufficient to prevent chronic fatigue and he is grouchy most of the day. He has lost a good deal of his appetite for meals, and has cut down in the variety of foods he will tolerate; his mother has to urge him increasingly. He may play for a few minutes with a new toy or household object, but he soon tires of it, throws it aside impatiently and whines or cries with outstretched arms to be carried. Now, even when he is carried, he is not content for long. But if his mother puts him down or tries to postpone picking him up in the first place, he yells loudly and she feels compelled to give in.

The past history shows that he had severe colic both afternoon and evening from the age of 2 weeks until 3 months. The mother, distressed by his agony, found that picking him up and walking him relieved him temporarily and asked the pediatrician whether this was right. He assured her that it was. By the age of 3 months it was apparent that painful colic had become infrequent, but the baby still cried in the afternoon and evening unless he was held. The cry was no longer that of pain but more of indignation and rage. The mother did not know how to extricate herself. She was kindhearted in the extreme and was made miserable by the child's crying. By nine months her patience has worn thin and she is exhausted from constant walking, carrying a heavy baby and lack of sleep. It does not help that her husband can sleep soundly all night and ask casually in the morning how things went.

There are many variations in this picture. Though the origin is most commonly in a colicky early infancy, there are other cases which begin later. One started with a painful ear infection at the age of 8 months and a number began between 4 and 12 months in babies who had previously been excellent sleepers and then started to wake suddenly with crying at night, possibly due to the pain of teething. The mother naturally took pity on the crying child and found she could sooth him by walking; he gradually learned how to stay awake and demand more of it. In some cases the difficulty is entirely in getting the child to go to sleep in the evening and he never wakes afterward during the night. One baby learned to stay awake until midnight. Other babies allow themselves to be put to bed willingly enough in the beginning but wake one to five times during the night. The etiologic factors common to all of these cases, aside from colic or some other painful disturbance, are a determined type of baby and a gentle, uncertain, long-suffering type of mother. Whether the baby was born with a determined temperament or gradually became so from his successful bullying cannot be told; no doubt both

factors operate. The mothers have been not only naturally sympathetic but they have also been disciples of the philosophy that the baby should be comforted when he cried.

Since the crucial factor in the picture is the mother's basic uncertainty, which makes it difficult for her to set sensible limits, the physician's long-term job is to help her acquire confidence in herself, and a sense of balance in managing her child. (In some cases a skilled psychiatrist may be of great assistance in helping her to understand and dispose of the origins of her insecurity, but such a psychiatric referral must be approached gradually and tactfully.) In all his contacts the physician should be uncritical, friendly, reassuring, to avoid giving her new cause for uneasiness. In his routine recommendations, whether for diet or toilet training or treatment of bronchitis, he should be unarbitrary, lest she get the idea that there is one perfect method; he should explain casually how far to go in following out a procedure lest she carry it to extremes.

The treatment of the sleep problem in the baby less than 1 year of age is relatively easy. The physician explains that, though the baby was in pain at the onset of the difficulty and though the mother was right in comforting him, the problem is now something else. He points out that a baby of this determined type who particularly enjoys company and motion can learn in relatively short order to keep himself awake. To keep his mother walking becomes a challenge, a tug of war. The more she tries to put him down and the more he succeeds in preventing this, the more he is stimulated to go on. The physician emphasizes that this success not only does not comfort the baby in the long run but becomes a strain to him. The mother is advised to lead up to bedtime with her usual attentions and affections, then to lay the baby in his bed calmly, serenely, firmly, and walk out of the room. The mother usually asks how long she should let the crying go on and a limit of 45 minutes is suggested for the sake of the exceptional baby who only becomes more hysterical the longer he cries.

One mother whose baby had carried this pattern up to the age of about 1½ years was advised to give the child a little lecture in friendly but firm tones at the time she put him to bed to the effect that it was now bedtime, he needed his rest, she needed hers, and he must go to sleep without any further fuss. This mother reported back in amazement the next day that after the firm talking-to he went right off to sleep without a whimper, for the first time in a year. No doubt the talk had a firming effect on the mother as well as an impressive effect on the baby. This kind of firm short lecture has been recommended in subsequent problems with younger infants, too.

Even a child 6 months of age can probably be impressed by a mother's tone of voice which implies that she has turned over a new leaf and means business. Most of these babies do not give in so easily but cry indignantly from 10 to 20 minutes the first night and perhaps 5 to 10 minutes the second night. A great majority of them have been cured within two nights. A beneficial cycle is established. The baby and mother both nearly double their nighttime rest and immediately show the good effects of this in their better spirits in the daytime. The babies who have miserable appetites promptly begin to eat more, and this further helps their daytime spirits and their nighttime sleepiness. The mothers are tremendously grateful and make a point of the fact that their enthusiasm and affection for the baby has returned with a rush.

It should be emphasized that this policy of letting the baby "cry it out" is recommended only for one particular disturbance: chronic resistance to sleep in the infant up to the age of 1 or 1½ years. The baby who unexpectedly wakes and cries from some

discoverable or undiscoverable misery is another matter, as is the child 2 years of age who suddenly becomes panicky at bedtime. The latter is suffering from an acute anxiety state which needs the most reassuring kind of treatment.

Inexperienced parents should start with the feeling that it is generally right to comfort an unhappy or uncomfortable infant. It is then the physician's job to pick up the occasional case of the baby who is developing the wrong habit from his mother's considerateness and to readvise her accordingly. The time to be particularly on the lookout is when colic is subsiding at about 3 months of age.

The business of wanting to be carried about all day, which is not present in all these sleep problems, may not, if it has become well established over a period of months, yield as promptly to treatment. The mother is encouraged to show an ample amount of affection and friendliness to the baby during the day, but to avoid picking him up for play except just before meals. At other times when she feels like being friendly she is advised to sit down beside him on the floor or sofa rather than to carry him around. Thus he gets her nearness and full attention without the stimulus to keep her walking. When he gets bored with her company, he can creep away and find other amusements. On the other hand, if she has him in her arms, even though he has become bored, he is enraged by her act of putting him down. She is advised to go about her housework, letting him creep after her if he wishes, or moving him from crib to play pen to carriage so that he may be in the room with her, if he cannot move himself about. But when he whimpers or raises his arms she is encouraged to explain cheerfully, affectionately but firmly that she is busy, and to give him some toy capable of amusing him. The mother must be warned that the solution of this extreme daytime dependence will not occur promptly but will come gradually if she follows directions and maintains the combination of firmness and affection.

These sleep problems of the first year of life seem to be attributable to the fact that the mother who is uncertain and insecure to start with is further encouraged to give in to her baby's even unreasonable demands by the official philosophy of which she has read and which her physician may have explicitly prescribed. There is nothing wrong with the philosophy in general and this article does not advocate a return to coldheartedness in child care. It is only that no philosophy can be translated into day by day and hour by hour practical application by an inexperienced person, and no two persons will interpret a philosophy exactly the same. The physician who guides mothers cannot get ideal results with generalizations alone any more than he can get them with arbitrary detailed instructions, the purposes of which are unclear. The pediatrician is closer to his patients than most other specialists and he has the opportunity, if he is reasonably sensitive and understanding, to slant the emphasis of his advice so that it fits the temperament of the parents, the temperament of the child and the latter's stage of development.

REFERENCE

1. Simsarian, F. P., and McLendon, P. A., Feeding behavior of infant during first 12 weeks of life on self-demand schedule, J. Pediat. **20**:93, 1942.

SPANISH ABSTRACT

Resistencia Crónica para el Sueño en la Infancia

La resistencia crónica para dormir en la infancia es un problema de comportamiento que aumenta frecuentemente y el que parece tener relación con el curso de la regulación propia y la confusión en la aplicación de esta filosofía.

Un problema moderno típico es la madre incierta y demasiado concienzuda, una discipula de la filosofía de expresión propia, que deja que su niño aprenda a resistir el sueño o a despertarse durante la noche y que llore hasta que se le coja.

A esta madre se le recomienda que acueste a su niño cariñosamente, pero con palabras firmes y que salga del cuarto. Generalmente tres noches de este tratamiento es suficiente para curar el problema del sueño.

La política de dejar que el niño llore hasta que se duerma se recomienda solamente en casos de resistencia crónica para dormir en el infante de 1 ó 1½ años de edad. No es para el niños que despierta porque está enfermo o incómodo o que sufre de un estado de ansiedad agudo.

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PANCREATIC FUNCTION IN SCARLET FEVER

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AMONG children with retarded development it is not uncommon to find cases in which the output of pancreatic enzymes is below the normal. There is no doubt that part of them are due to congenital conditions, syphilis or cystic fibrosis. These manifest themselves mostly in the early months of life. There are, however, a number of patients who had thrived well for many years before they suddenly stopped growing and putting on weight. The complaint is usually ascribed by the parents to some infectious disease and there are certainly cases in which such a connection could, with more or less certainty, be established. It is possible that involvement of the pancreas, or at least some disturbance of its excretory function, might be more frequent in some diseases than is commonly supposed. Most cases remain unnoticed, especially if the disturbance does not present the stormy symptoms usually attributed to the acute inflammation of the pancreas.

A number of reports have been published on pancreatic function in infectious diseases. The bulk of the literature deals with the output of enzymes in epidemic parotitis. There are a few observations of sporadic cases, mostly severe ones, in which pancreatitis occurred as a complication of various other infections. The author had occasion to observe several patients in whom the failure to develop could be explained by pancreatic dysfunction and in whom this condition seemed to have started during or following some acute infectious disease;[1] in one child it followed scarlet fever. Goldie[2] reported a case of pancreatitis as a complication of that infection and it is evident, from the reports of Otto,[3] Racugno and Manca,[4] and especially of Gülzow,[5] who found steatorrhea in 50% of his patients suffering from scarlet fever, that in this disease pancreatic dysfunction of a greater or lesser degree is a common occurrence. As, however, no systemic examination of the duodenal juice was made, the exact nature and the probable outcome of the complication is unknown. For this reason the observations reported here were undertaken.

METHODS

Collection of fluid was made by the aid of 2 tubes and aspiration by a syringe every 10 min. Specimens were kept on ice until the examination, which always took place within an hr.

In analysis of duodenal contents, the following methods, whose details were reported in a previous paper,[6] were used:

1. Amylase: Wohlgemuth's[7] iodometric determination and Ågren and Lagerlöf's[8] method.
2. Trypsin: Michaelis'[9] casein method and Fermi's procedure, a modification of Andersen and Early[10]
3. Lipase: Willstätter's[11] and Freudenberg's[12] titrimetric methods.

Determination of enzymes in the blood were carried out by the following procedures:

1. Amylase, Somogyi's method.[13]
2. Lipase, Cherry and Crandall's [14] method, in the modification of Comfort and Osterberg.[15]

There being no means for comparing different values yielded by different methods of enzyme

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TABLE I

LOWEST AND HIGHEST LIMITS OF NORMAL RANGE YIELDED BY DIFFERENT METHODS

Enzyme	Method	Limit of Normal Range		Unit
		Lowest (%)	Highest (%)	
Amylase	Wohlgemuth[7]	160	204,800	dilution
	Ågren and Lagerlöf[8]	0.33	245	gm. maltose/ml. of juice
Trypsin	Michaelis[9]	128	102,400	dilution
	Andersen and Early[10]	0.01	0.25	dilution (Tube nos. 4 and 2)
Lipase	Willstätter[11]	13	5,300	19.8 ml. $\frac{n}{10}$ KOH*
	Freudenberg[12]	3.0	850	ml. of $\frac{n}{10}$ NaOH/5 ml. of milk/1 ml. solut. 2 hr.
Serum amylase	Somogyi[13]	60	20,000	original
Serum lipase	Cherry and Crandall[14]	0.2	150	ml. of $\frac{n}{20}$ NaOH/ml. of serum

* Using a standard olive oil with a saponification number of 185.5.

assay, it seemed serviceable to express any figure below the normal in per cent of the lowest possible limit of the normal range, and values above the normal in per cent of the upper limit of the normal. According to examinations reported in a previous paper,[15] these units are as seen in Table I.

The values of Somogyi's and Cherry and Crandall's methods, established by previous examinations, are in full accordance with the observations of Somogyi,[16] Heifetz,[17] and Comfort.[18]

All determinations were made in duplicate or triplicate.

MATERIAL

Thirty-two children, 18 male and 14 female, suffering from scarlet fever were examined. Their ages varied from 18 mos. to 16 yrs.; the average was 6 7/12 yrs. They were all above the height and weight standards of their respective age groups. Before their illness, all were free of complaints, showed a negative response to intradermal tuberculin, gave negative complement fixation tests for syphilis, had a good appetite and had no digestive anomalies. All children examined were admitted to the hospital at the onset of their illness, at most 24 hrs. after the appearance of the first symptoms.

Of the 32 children, 10 had complications, such as nephritis, otitis, myocarditis and lymphadenitis. One died, while all the others were discharged completely recovered (see Table II).

OBSERVATIONS

Duodenal tubings and blood examinations were undertaken every 2nd or 3rd day in the first 3 wks.; and then, if no abnormal conditions were found, every 5 days or once a week.

In 6 children (Cases 3, 4, 15, 21, 28 and 30), the enzymes were always found normal throughout the whole period of the illness.

In 26 children some abnormality of pancreatic enzyme function could be demonstrated. Pathologic values for all the 3 enzymes were encountered in 14, for both trypsin and lipase in 6, for trypsin alone in 1, and for lipase alone in 5 patients. Thus, there was a dysfunction of the amylase output in 14 children, of trypsin in 21, and of lipase in 25 children.

The dysfunction, in most of the cases, had a strikingly regular pattern. Of the 14 cases in which the output of all 3 enzymes was affected, 10 showed that pattern. Their values are recorded in Table III and a diagram was also constructed on the basis of the daily mean values. (See Fig. 1.)

As can be seen from Table III and Fig. 1. in the first days of the disease, i.e., in the exanthematous stage, the output of pancreatic enzymes was found increased from 3 to 5 times the upper limit of the normal range, while enzymes in the blood decreased to about half of the lowest limit of the normal. Then, at about the end of the 1st wk., a sudden change occurred. The activity of enzyme in the duodenal juice decreased much below the normal; the fall was most pronounced in the lipase values. At the same time, both amylase and lipase in the blood, but especially the former enzyme, attained

TABLE II

MATERIAL, COMPLICATIONS, DYSFUNCTIONS OBSERVED

Case	Name	Sex	Age		Complications	Dysfunctions		
			Yrs.	Mos.		Amylase	Trypsin	Lipase
1	SM	f	1	6	lymphadenitis, otitis	+	+	+
2	TS	m	1	7	—	+	+	+
3	SG	m	2		otitis			
4	HJ	m	2	6	—			
5	SA	m	2	6	—	+	+	+
6	RI	f	3		—		+	
7	SA	m	3	6	otitis, nephritis		+	+
8	KL	m	3	10	dehydration, acidosis	+	+	+
9	NJ	m	4		—	+	+	+
10	HJ	f	4		myocarditis		+	+
11	GJ	m	4	1	lymphadenitis			+
12	LG	m	4	4	—			+
13	GT	m	4	6	otitis		+	+
14	HI	f	5		otitis	+	+	+
15	ME	m	5		—			
16	PL	m	5	2	—			+
17	SG	m	5	5	—	+	+	+
18	BM	f	6		—		+	+
19	BG	m	6		—	+	+	+
20	MA	f	6	2	nephritis, pneumonia, septicemia	+	+	+
21	LE	f	7		—			
22	DT	f	8		—			+
23	RV	f	8	7	—	+	+	+
24	KP	m	9		—	+	+	+
25	MA	m	10		—		+	+
26	RM	f	11		—	+	+	+
27	BJ	m	11		—			+
28	BP	m	11		—			
29	HD	f	12		lymphadenitis		+	+
30	NE	f	12		otitis			
31	OE	f	12		—	+	+	+
32	NM	f	15		—	+	+	+

exceptionally high levels. Conditions began to return to normal in the middle of the 3rd wk. when both pancreatic amylase and blood lipase levels were within the normal range. Complete cessation of the dysfunction, however, did not occur before the middle of the 4th wk. It was at this time that the abnormally low pancreatic lipase and high blood amylase values returned to their original levels.

A similar sinusoid curve, although of a flatter shape, characterized the activity of trypsin and lipase in 4 (Cases 7, 13, 18 and 25) of the 6 patients in whom amylase was always found normal, and also the level of lipase in 4 (Cases 11, 12, 22 and 27) of the 5 cases in which the dysfunction was confined to that enzyme. Enzymes in the blood in 3 (Cases 7, 18 and 22) behaved in the same

manner as it did in the 10 patients reported in Table III, except that both the same initial fall and the subsequent rise were much less pronounced; in 2 cases (Cases 12 and 22), the changes restricted themselves to lipase alone, while in the 3 others (Cases 11, 13 and 25) both enzymes remained normal.

A single case (Case 6) was found in which trypsin was the only enzyme affected. Its activity fell, without previous increase, to below 50% on the 10th day and remained between 40 and 70% until the 17th day when it became normal again. In this case there was no change whatever in the enzymes in the blood. A similar dysfunction was observed in Case 10, in which both trypsin and lipase were affected, and in Case 16, where lipase was the only enzyme involved, and, further, also in Case 32, in which patient there was no initial rise but a sharp fall in all the 3 enzymes in the

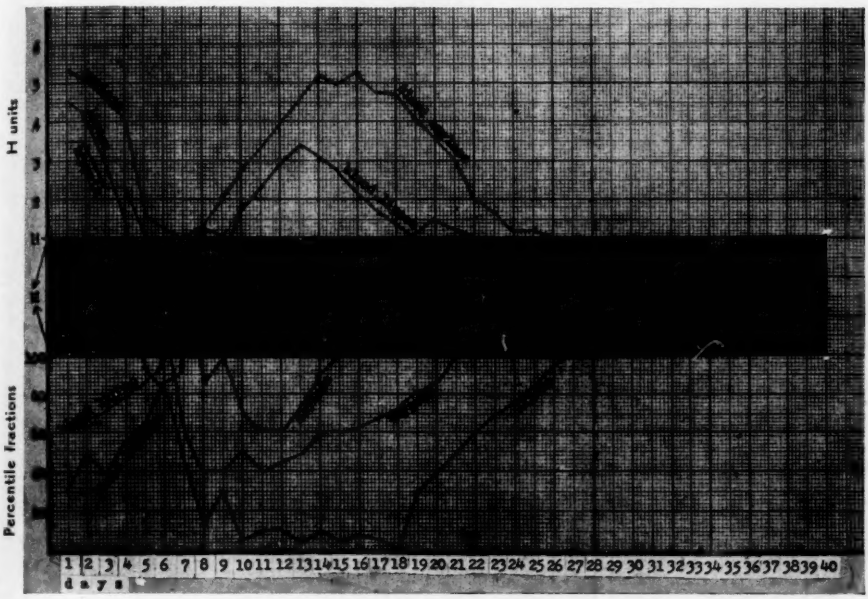

FIG. 1. Daily mean values of Table III.

duodenal juice on the 8th day with almost no increase of the enzymic levels in the blood. Conditions in this last case returned to normal quickly.

Four further cases have to be discussed separately. One of them (Case 8), a boy of 4 yrs., was admitted in a state of extreme dehydration and acidosis on the 3rd day of his illness. Duodenal tubing next day revealed extremely high values for all the 3 enzymes (amylase, 960%; trypsin, 490%; lipase 610%). The fluid output was, however, diminished to such an extent that no more than 3 ml. of thick juice could be aspirated from the duodenum in 50 min. Then secretin was administered intravenously. Following this, 14 ml. of duodenal contents were collected within 15 min.; enzyme values in this juice were only slightly above the normal. The patient was rehydrated in 3 days and then all pancreatic enzymes were within the normal range. Thereafter, apart from a slight decrease of lipase activity from the 12th to the 18th day, no abnormality was noted. Unfortunately, no determinations of enzymes in the blood were performed in this case.

Another child (Case 20), a girl of 6 yrs. who was admitted on the 1st day of illness, developed nephritis on the 3rd day, mastoiditis on the 12th and pneumonia and septicemia on the 25th day. She died on the 29th day. The 1st enzyme determinations were made on the 3rd day when there was already almost a complete lack of lipase, while amylase and trypsin values were still normal. In the blood, lipase was about half of the lowest limit of normal at that time, and the level of amylase

was normal. A week afterwards, both trypsin and lipase were lacking in the duodenal juice and amylase amounted to only 20% while in the blood amylase was 50% and lipase 18%. Two more determinations were made, one on the 18th, and another on the 24th day; both yielded unchanged results. Autopsy revealed extensive hemorrhages in the pancreas, with cloudy swelling and necroses of the parenchyma.

Cases 24 and 29, those of a male child of 9 and a female of 12 yrs., deserve special attention as it was thought that in these not only a dysfunction but a real inflammation of the pancreas occurred. Typical pain and tenderness on palpation were present in the 1st child, but in the other no abdominal symptoms could be found. The secretory changes ran almost parallel in the 2 cases. At

TABLE III

Enzyme Values in 10 Cases

Case No.	Enzyme	Day of Illness																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	A	600*	—	—	400*	—	200*	M	—	—	70	—	—	80	—	M	—	—	M	—
	T	400*	—	—	200*	—	M	70	—	—	40	—	—	40	—	50	—	—	80	—
	L	500*	—	—	200*	—	M	60	—	—	ø	—	—	10	—	ø	—	—	ø	—
	BA	40	—	45	—	—	70	M	—	—	300*	—	—	600*	—	600*	—	—	400*	—
	BL	70	—	80	—	—	80	80	—	—	200*	—	—	400*	—	300*	—	—	M	—
2	A	—	400*	—	—	—	M	—	90	—	—	—	60	—	—	—	M	—	—	M
	T	—	400*	—	—	—	M	—	50	—	—	—	50	—	—	—	70	—	—	80
	L	—	500*	—	—	—	80	—	20	—	—	—	ø	—	—	—	20	—	—	ø
	BA	—	30	—	—	—	M	—	200*	—	300*	—	500*	—	—	—	700*	—	—	400*
	BL	—	50	—	—	—	M	—	M	—	M	—	300*	—	—	—	400*	—	—	M
	A	800*	700*	700*	—	200*	90	—	—	M	—	70	—	—	M	—	—	M	M	—
	T	500*	400*	300*	—	M	M	—	—	40	—	50	—	—	50	—	—	80	70	—
	L	400*	500*	400*	—	M	70	—	—	30	—	10	—	—	10	—	—	20	ø	—
	BA	20	30	30	—	60	90	—	M	—	—	300*	—	—	700*	500*	—	500*	400*	—
	BL	50	90	70	—	90	M	—	M	—	—	200*	—	—	300*	300*	—	M	200*	—
9	A	500*	—	300*	—	M	—	—	70ø	—	—	—	60	—	—	—	M	—	—	M
	T	300*	—	200*	—	M	—	—	30	—	—	—	40	—	—	—	70	—	—	M
	L	300*	—	300*	—	M	—	—	ø	—	—	—	20	—	—	—	10	—	—	30
	BA	20	—	50	—	80	—	—	M	—	—	—	400*	—	—	—	400*	—	—	400*
	BL	80	—	70	—	80	—	—	200*	—	—	—	300*	—	—	—	M	—	—	M
14	A	—	500*	—	500*	—	—	M	—	—	80	—	—	—	M	—	M	—	—	M
	T	—	300*	—	200*	—	—	50	—	—	30	—	—	—	60	—	60	—	—	70
	L	—	400*	—	M	—	—	70	—	—	ø	—	—	—	10	—	ø	—	—	20
	BA	—	70	—	60	—	—	80	—	—	200*	—	—	—	400*	—	500*	—	—	300*
	BL	—	70	—	90	—	—	M	—	—	300*	—	—	—	300*	—	M	—	—	M
17	A	—	500*	—	300*	—	—	M	—	—	60	—	—	—	60	—	M	—	—	M
	T	—	400*	—	300*	—	—	60	—	—	60	—	—	—	70	—	50	—	—	80
	L	—	400*	—	200*	—	—	30	—	—	ø	—	—	—	ø	—	ø	—	—	40
	BA	—	40	—	50	—	—	70	—	—	M	—	—	—	500*	—	400*	—	—	400*
	BL	—	80	—	70	—	—	200*	—	—	M	—	—	—	200*	—	200*	—	—	M
19	A	400*	—	400*	—	—	M	—	—	—	80	—	—	70	—	—	90	—	—	M
	T	300*	—	200*	—	—	M	—	—	—	30	—	—	60	—	—	70	—	—	90
	L	600*	—	300*	—	—	80	—	—	—	20	—	—	ø	—	—	10	—	—	40
	BA	20	—	40	—	80	—	M	—	—	200*	—	—	500*	—	—	400*	—	—	300*
	BL	50	—	80	—	M	—	90	—	—	200	—	—	200	—	—	300	—	—	M
23	A	500*	—	—	—	300*	—	M	—	—	—	60	—	—	—	M	—	—	M	—
	T	400*	—	—	—	M	—	60	—	—	—	30	—	—	—	70	—	—	80	—
	L	500*	—	—	—	80	—	30	—	—	—	ø	—	—	—	10	—	—	ø	—
	BA	50	—	30	—	60	—	M	—	200*	—	400*	—	500*	—	500*	—	—	400*	400*
	BL	40	—	70	—	90	—	M	—	M	—	300*	—	400*	—	200*	—	—	M	—
26	A	300*	300*	—	—	M	—	—	M	—	—	50	—	—	80	—	—	M	—	—
	T	200*	300*	—	—	M	—	—	40	—	—	40	—	—	50	—	—	70	—	—
	L	400*	300*	—	—	90	—	—	ø	—	—	20	—	—	30	—	—	ø	—	—
	BA	30	30	—	—	60	—	—	M	—	—	300*	—	—	500*	—	—	400*	—	—
	BL	70	60	—	—	M	—	—	90	—	—	200*	—	—	200*	—	—	200*	—	—
31	A	—	600*	400*	—	200*	—	—	80	—	60	—	—	—	M	—	—	M	—	M
	T	—	300*	200*	—	M	—	—	30	—	40	—	—	—	60	—	—	60	—	70
	L	—	400*	200*	—	M	—	—	30	—	10	—	—	—	ø	—	—	ø	—	50
	BA	—	80	30	—	50	—	—	M	—	300*	—	—	—	400*	—	—	500*	—	300*
	BL	—	40	60	—	50	—	—	M	—	M	—	—	—	500*	—	—	200*	—	M
Mean:	A	530*	500*	450*	400*	160*	120	M	85	M	70	60	60	75	90	M	M	M	M	M
	T	350*	350*	230*	230*	M	M	60	40	40	50	40	45	50	60	60	64	70	76	81
	L	450*	420*	300*	170*	94	82	48	13	30	06	10	10	05	10	05	08	07	ø	30
	BA	30	48	38	55	65	86	90	120*	200*	270*	330*	450*	530*	500*	530*	480*	470*	400*	360*
	BL	60	67	71	80	85	93	110*	120*	M	170*	230*	300*	330*	300*	270*	220*	170*	130*	M

TABLE III—*Continued*

Case No.	Enzyme	Day of Illness																		
		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
1	A	—	—	M	—	—	M	—	—	—	M	—	—	—	—	M	—	—	—	M	—
	T	—	—	M	—	—	M	—	—	—	M	—	—	—	—	M	—	—	—	M	—
	L	—	—	90	—	—	M	—	—	—	M	—	—	—	—	M	—	—	—	M	—
	BA	—	—	M	—	—	M	—	—	—	200*	—	—	—	—	M	—	—	—	—	—
	BL	—	—	M	—	—	M	—	—	—	—	—	—	—	—	M	—	—	—	—	—
2	A	—	M	—	—	M	—	—	—	M	—	—	—	M	M	—	—	M	—	—	—
	T	—	M	—	—	M	—	—	—	M	—	—	—	M	M	—	—	M	—	—	—
	L	—	50	—	—	M	—	—	—	M	—	—	—	70	M	—	—	M	—	—	—
	BA	—	200*	—	—	M	—	—	—	M	—	—	—	M	M	—	—	—	—	—	—
	BL	—	M	—	—	M	—	—	—	—	—	—	—	M	—	—	—	—	—	—	—
5	A	M	—	—	—	M	—	—	—	M	—	—	—	M	—	—	—	—	—	—	—
	T	M	—	—	—	M	—	—	—	M	—	—	—	M	—	—	—	—	—	—	—
	L	40	—	—	—	M	—	—	—	M	—	—	—	M	—	—	—	—	—	—	—
	BA	200*	—	—	M	—	—	—	M	—	—	—	—	—	—	—	—	—	—	—	—
	BL	M	—	—	M	—	—	—	M	—	—	—	—	—	—	—	—	—	—	—	—
9	A	M	—	—	M	—	—	M	—	—	M	—	—	—	—	—	M	—	—	—	—
	T	200*	—	—	M	—	—	M	—	—	M	—	—	—	—	—	M	—	—	—	—
	L	80	—	—	80	—	—	M	—	—	M	—	—	—	—	—	M	—	—	—	—
	BA	200*	—	—	M	M	—	—	—	—	—	M	—	—	M	—	—	—	—	—	—
	BL	M	—	—	80	M	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
14	A	M	—	—	M	—	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—
	T	90	—	—	M	—	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—
	L	70	—	—	80	—	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—
	BA	M	—	—	200*	—	—	—	—	M	—	—	—	M	—	—	—	—	—	—	—
	BL	200*	—	—	M	—	—	—	—	M	—	—	—	M	—	—	—	—	—	—	—
17	A	—	M	—	—	M	—	—	—	M	—	—	—	—	—	M	—	—	—	—	—
	T	—	M	—	—	M	—	—	—	M	—	—	—	—	—	M	—	—	—	—	—
	L	—	60	—	—	90	—	—	—	M	—	—	—	—	—	M	—	—	—	—	—
	BA	—	M	—	—	—	M	—	—	—	—	—	M	—	—	—	—	—	—	—	—
	BL	—	M	—	—	—	70	—	—	M	—	—	M	—	—	—	—	—	—	—	—
19	A	—	M	—	M	—	—	—	—	M	—	—	—	—	—	—	—	M	—	—	—
	T	—	M	—	M	—	—	—	—	M	—	—	—	—	—	—	—	M	—	—	—
	L	—	70	—	70	—	—	—	—	M	—	—	—	—	—	—	—	—	—	—	—
	BA	—	M	—	M	—	—	—	—	M	—	—	—	—	—	—	—	M	—	—	—
	BL	—	M	—	M	—	—	—	—	—	—	—	—	—	—	—	—	M	—	—	—
23	A	—	—	M	—	—	M	—	—	—	—	—	—	—	M	—	—	—	—	—	—
	T	—	—	M	—	—	M	—	—	—	—	—	—	—	M	—	—	—	—	—	—
	L	—	—	70	—	—	90	—	—	M	—	—	—	—	M	—	—	—	—	—	—
	BA	—	—	M	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—	—	—
	BL	—	—	M	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—	—	—
26	A	—	—	200*	—	M	—	M	—	—	—	—	—	M	—	M	—	—	—	—	—
	T	—	—	M	—	M	—	—	—	—	—	—	—	M	—	—	—	—	—	—	—
	L	—	—	80	—	80	—	M	—	—	—	—	—	80	—	M	—	—	—	—	—
	BA	—	—	200*	—	M	—	M	—	—	—	—	—	—	—	—	—	—	—	—	—
	BL	—	—	M	—	M	—	M	—	—	—	—	—	—	—	—	—	—	—	—	—
31	A	M	—	M	—	200*	—	M	—	—	—	—	—	—	—	—	—	—	—	—	—
	T	M	—	M	—	M	—	M	—	—	—	—	—	—	—	—	—	—	—	—	—
	L	10	—	30	—	50	—	M	—	—	—	—	—	—	—	—	—	—	—	—	—
	BA	300*	—	M	—	M	—	200*	—	—	M	—	—	—	M	—	—	—	—	—	—
	BL	M	—	M	—	M	—	M	—	—	M	—	—	—	M	—	—	—	—	—	—
Mean:	A	M	M	M	M	M	M	M	—	M	M	—	—	M	M	M	M	M	—	—	M
	T	120*	M	M	M	M	M	M	—	M	M	—	—	M	M	M	M	M	—	—	M
	L	50	60	68	76	84	95	M	M	M	M	—	—	80	M	M	M	M	—	—	M
	BA	200*	170*	120*	120*	M	M	150*	M	M	150*	M	M	M	M	M	—	M	—	—	—
	BL	120*	M	M	95	M	90	M	M	M	M	—	M	M	M	M	—	M	—	—	—

Abbreviations: A—Amylase in duodenal juice L—Lipase in duodenal juice BL—Lipase in blood
T—Trypsin in duodenal juice BA—Amylase in blood M—Normal value
Per cent of the upper limit of normal; ordinary figures indicate per cent of lowest limit of normal.

first, on the 2nd day, instead of an increase there was a decrease in the concentration of all 3 pancreatic enzymes but unusually large amounts of duodenal juice, 40 to 70 ml., could be aspirated in 30 to 40 min. The values of serum amylase and lipase were much above the normal. In the 1st child determinations yielded 700% for amylase and 510% for lipase on the 2nd day, 610% and 420% on the 5th, and 720% and 410% on the 8th. Conditions were the same on the 10th day. On the 15th day, however, practically no trypsin and lipase were found in the duodenum and there were only traces of amylase (16%), while in the serum amylase amounted to 56% only and lipase to 33%. The dysfunction remained unchanged until the beginning of the 4th wk. when it slowly began to improve.

Both children made a full recovery. This is, in all probability, the manner in which cases of celiac syndrome due to secondary pancreatitis originate.[1]

It seemed from most patients examined on the 1st day of scarlet fever as if the enzymic changes would have preceded the appearance of the enanthem and the exanthem. It is not known exactly when the pancreatic dysfunction begins. There was opportunity to examine 3 patients in the incubation period. A dysfunction less marked but otherwise similar to the one described above was observed in a child 2 days before the rash appeared and in another 1 day before the exanthem. The 3rd child, 1 day before the eruption, had normal enzyme levels in the duodenal juice. Blood enzymes were not determined in this case. Unfortunately, neither of the children could be observed during the subsequent course of the illness.

Comment

It seems from the above that pancreatic dysfunction is often associated with scarlet fever. The dysfunction, as had already been stated by Hess,[19] is not due to fever. Most of the above children were afebrile just when the hypofunction reached its most severe degree. It is also apparent from Table III that the "second illness" did not alter the output of enzymes; and, further, from the comparison of Table II and Fig. 1, that the dysfunctions observed were in no connection with eventual complications occurring during the course of, or associated with, scarlet fever.

In accordance with several authors, it was proved in a previous paper[12] that in healthy children a strict parallelism exists in the secretion of the three pancreatic enzymes. This phenomenon is entirely changed in children suffering from scarlet fever. Not only may the activity of a certain enzyme be entirely lacking or its activity decreased while, at the same time, one or both of the others are being normally secreted; but even the fluctuations of the single enzymes within a short experimental period are not parallel. The lack of parallelism may persist for a time after the activity of the enzymes had returned to normal. In fact, it seems to be the most sensitive, and in some cases the only, indicator of pancreatic dysfunction.

The origin of the dysfunction remains unknown. The common histologic picture seen in the pancreas during scarlet fever is that of cloudy swelling and, in grave cases, extensive hemorrhages and necroses may appear (Eichhorst,[20] Dieckhoff, [21] Schlesinger,[22] and Gruber[23]). Similar changes were found in Case 20, the only lethal case in the present material. These facts, however, do not solve the problem, i.e., to what effects the disturbances of enzyme function are due.

Summary

Determinations of enzymes in both the duodenal juice and the blood were undertaken in 32 children suffering from scarlet fever. Abnormal values were found in 26 patients. In 10 of these, the dysfunction showed a regular pattern. In the first days, the output of pancreatic enzymes was found high above the normal while those in the blood decreased. After the first week the activity of enzymes in the duodenal juice decreased and at the same time the blood enzymes attained high levels. Conditions returned to normal in the fourth week. Similar, but less marked and incomplete changes, were found in three other children while in the rest incomplete dysfunctions or only hypofunction occurred. Of the three enzymes, the output of lipase was the one most frequently and most severely affected.

In two patients the symptoms observed pointed to an inflammation of the pancreas.

The dysfunctions were in no connection with either fever or complications. In most cases there was no parallelism in the secretion of the single enzymes.

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SPANISH ABSTRACT

Función Pancreática en la Escarlatina

Se llevaron cabo determinaciones de enzimas en el jugo duodenal y en la sangre de 32 niños con escarlatina. Se encontraron trazas anormales en 26 pacientes. En 10 de éstos la disfunción fué de carácter ordinario. Los primeros días la producción de los enzimas pancreáticos en el jugo duodenal disminuyó, y al mismo tiempo los enzimas de la sangre alcanzaron niveles altos. Las condiciones se normalizaron a la cuarta semana. Cambios similares, pero menos marcados e incompletos se encontraron en otros tres niños, mientras que en el resto ocurrieron disfunciones incompletas o sólo hipofunción. De los tres enzimas, la producción de lipasa fué la más frecuente y severamente afectada.

En dos pacientes los síntomas que se observaron denotaban una inflación del pancreas.

Las disfunciones no tenían conexión alguna con la fiebre ni con las complicaciones. En la mayor parte de los casos no hubo paralelismo en la secreción de los diferentes enzimas.

Bokay Janos-Utca 53

ANAPHYLACTOID PURPURA COMPLICATED BY AN IRREDUCIBLE INTUSSUSCEPTION

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ABDOMINAL symptoms and signs which occur during the course of purpura are now well recognized among the protean manifestations. The occurrence of intussusception complicating purpura does not occur frequently. Sutherland[1] in 1904 was the first to call attention to the possibility of intussusception complicating purpura. The patient, a girl aged 7 years, was admitted to the hospital with a diagnosis of Henoch's purpura. A complicating intussusception was not diagnosed but at necropsy an irreducible intussusception, the cecum and ileum being invaginated into the colon for about 10 cm., was found. The mass was adherent and gangrenous in appearance. Lett[2] was the first to perform a laparotomy for intussusception complicating purpura. The patient, a male child 3 years of age, had an intussusception of the ileocecal type which was easily reduced. Three days after operation, a recurrence of abdominal pain due to another intussusception was noted, but the child's condition did not allow further operative intervention and he died eight days postoperatively. Necropsy revealed a general septic peritonitis with an enteric intussusception 25.4 cm. from the ileocecal valve. It was 12.7 cm. long and irreducible. Bailey,[3] in an excellent review of 30 cases of abdominal purpura, found 14 had intussusception while 16 had only hemorrhage into the bowel wall at laparotomy. Bailey described two additional cases of his own; one, which was subjected to laparotomy, did not have an intussusception but showed a subserous hemorrhage involving about 121 cm. of the jejunum. The patient recovered. Of the 14 patients with intussusception complicating purpura in Bailey's review, nine were operated upon with a mortality of 11%, while for the five not operated upon, the mortality was 60%. In the operated group, three were male children, aged 4, 5 and 6 years, all required intestinal resection and all recovered. Schwartzman[4] subsequently reported an intussusception complicating Henoch's purpura in a child 3 years of age which was irreducible at laparotomy. Resection was performed but the child died the following day.

CASE REPORT

R. G., 3 yrs. of age, white male, was perfectly well until 22 days before admission when he developed a swelling of the left testicle to 3 times its normal size which subsided in 48 hrs. The next day he developed a swelling of the left ankle joint and, in a few days, the right ankle was similarly affected. A purpuric rash then appeared over both ankles and the clinical picture was attributed to an allergy since a blood count showed a marked increase in the eosinophiles. The arthritic and purpuric manifestations subsided in about 7 days. Fourteen days before admission, he vomited a number of times for the next 48 hrs. and this subsided. An enema revealed bright blood and this was followed by bloody stools and mucus. This ceased in 2 days but the child continued to vomit occasionally and have abdominal cramps. Two days before admission, he was weak, listless and unable to walk. He was seen on the 22nd day of his illness at the hospital. The patient was dehydrated, pale and listless, temperature 38.3° C., pulse 160/min., respirations 24/min. The abdomen was distended and visible peristalsis was seen at the periumbilical area. No masses could

From the Surgical and Pediatric Service of Harper Hospital, Detroit, Mich.
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be felt but on rectal examination there was some fulness in the cul-de-sac. RBC count 4.28 million, WBC 11.1 thousand, 80% neutrophiles, 10% lymphocytes, 9% monocytes and 1% basophiles, hgb. 10 gm./100 cc. Platelet count was 720,000; clotting time 3½ min.; bleeding time 2 min. A flat roentgenogram of the abdomen, with a Levin tube in the stomach, showed gaseous distention in the loops of the ileum; there was no evidence of gas in the cecum or remainder of the colon indicating an obstruction in the ileum (see Fig. 1).

A diagnosis of purpura with a complicating intussusception was made. During the next 24 hrs. after admission, Wangensteen gastric suction was instituted, the fluid and chemical balance restored and penicillin and streptomycin given intramuscularly every 3 hrs.

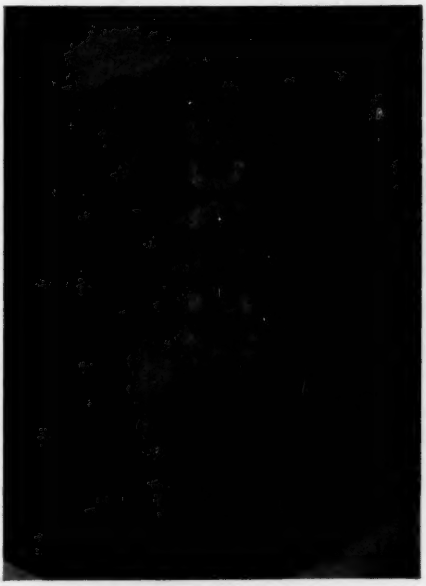

FIG. 1

The day following admission, a laparotomy was performed. Upon opening the peritoneal cavity, a moderate amount of clear amber fluid was encountered and a dilated loop of small bowel presented. This was found to be terminal ileum and tracing it downward an irreducible ileo-ileo intussusception was evident about 22 cm. from the ileocecal valve. There was evidence of local peritoneal reaction about the intussusception and after careful examination it was deemed irreducible. A resection was then performed of the entire mass. The proximal and distal ends of the ileum were closed and a side to side anastomosis performed in 3 layers. (See Figs. 2 and 3.) Five hundred cc. of blood were given during the operative procedure and the child's condition was good considering the lesion.

Pathologic report was as follows: *Gross:* On reduction of the specimen, which consisted of a piece of bowel 7 × 5 cm., it was found that the intussusceptum had perforated due to necrosis, but was walled off by the distal segment or intussuscipiens circumscribing it. In view of this it was fortunate that no forcible attempt at reduction was made at time of laparotomy. Microscopic examination revealed evidence of localized peritonitis at the site of intussusception.

Postoperatively, the patient was placed in an oxygen tent, Wangensteen suction continued and fluid and vitamin requirements met by intravenous infusions. The Levin tube was discontinued on the 4th postoperative day and clear fluids allowed by mouth. A soft diet was tolerated on the 6th postoperative day, the operative wound healed per primam and convalescence was uneventful. He was discharged from the hospital on the 11th postoperative day and is still well now 11 months later.

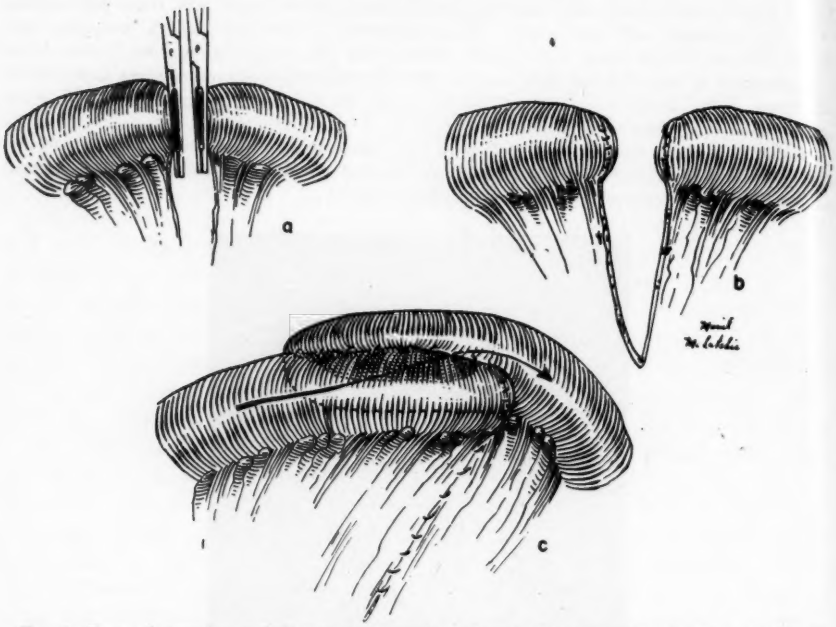

FIG. 2. Type of resection and lateral anastomosis performed. (From Allen, A. W., and Welch, C. E., Surgery of Small Intestine—Surgical Treatment, Philadelphia, J. P. Lippincott Company, 1947, p. 643, Fig. 306.)

FIG. 3. Excised specimen. Note probe inserted in perforation of intussusceptum.

Discussion

Purpura may be on an allergic basis in children,[5] the reaction being to foods or drugs. Observation on this patient early in the course of his purpura made this appear likely. Clinically, it is impossible to differentiate hemorrhage into the bowel wall and intussusception complicating purpura because both cause signs and symptoms of intestinal obstruction and both may be associated with a palpable mass. Laparotomy is therefore indicated early.

Summary

A case of anaphylactoid purpura complicated by an irreducible intussusception is reported. Resection and immediate intestinal anastomosis resulted in recovery.

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Spanish Abstract

Púrpura Anafilactoide Complicada por una Intususcepción Irreducible

Los síntomas abdominales y signos que ocurren durante el curso de la púrpura pueden ser debidos ya sea a una hemorragia en la pared del intestino o a una intususcepción. Hay que practicar la laparotomía si hay duda acerca la diagnosis correcta.

Un varoncito blanco de 3 años, 21 días antes de la admisión, tuvo una hinchazón en el testículo izquierdo, esto fué seguido por una hinchazón del tobillo izquierdo y después de algunos días del derecho. Un salpullido purpúrico apareció en ambos tobillos, el que desapareció en 10 días. Una lavativa reveló sangre viva, seguida por deposiciones con sangre y moco. El continuó con dolor abdominal, nausea y vómitos 12 días antes de la adminisión.

En la operación se encontró una intususcepción ileo-ileal irreducible. Se hizo una resección y una anastomosis lado a lado. El resultado patológico: El espécimen consistió de un pedazo de intestino 7 x 5 cm. y en la reducción se encontró que el intususceptum se había perforado debido a la necrosis; pero estaba alejado por el segmento distal o intususcipienses que lo limitaba. El paciente salió del hospital 11 días después de la operación y ya ha estado bien durante 11 meses.

David Whitney Building

BEDSIDE CABINET FOR THE NEWBORN INFANT DESIGNED FOR ROOMING-IN FACILITIES

By PRESTON A. MCLENDON, M.D., AND JOHN PARKS, M.D.
Washington, D.C.

IT IS necessary to provide convenient and practical methods of infant handling in adopting the principle of rooming-in and selective feeding procedures. This is important, since the mother plays a prominent role in the daily care of her infant. The infant must be available to her for a greater part of the day. She deserves consideration in the ease with which she can handle her infant. The carriage for the newborn infant, therefore, becomes an all important link in this service.

The bassinet in use on the maternity service at the George Washington University Hospital fills most of these requirements. In the over-all planning of this service, the bassinet was designed to fulfill the following demands: 1. simplicity; 2. ease of cleaning; 3. mobility—to move to and from the mother's room; 4. drawers and compartments to store bedside and nursery equipment sufficient for complete care of the infant; 5. foolproof attachment to the mother's bed in adjustable positions; 6. moveable bassinet on top of the cabinet for convenient and easy lifting-out and replacing the infant; 7. clear plastic bassinet for observation of the infant by nurse and mother.

The cabinet-bassinet is easily moveable and is provided with 5 inch casters. The cabinet is 19 inches wide, 28½ inches long and 30 inches deep (legs included) surmounted by the bassinet held in a frame which can be pulled laterally for a distance of 18 inches, just clearing the top of the mother's bed. This places the infant in such a position that, without strain or awkwardness, he can be lifted out by the mother. (In this position, the top of the cabinet can be used for temporary placement of the infant by the nurse while changing linen or cleaning the bassinet. This top is surrounded on three sides by a rod 4 inches above the cabinet level.)

The cabinet contains three compartments for storing clean linens and diapers for 24 or more hours of service. All inside seams are welded or molded flush so as to minimize dust collection. These compartments are protected by doors with piano hinges.

On either end of the cabinet above the compartments are drawers 14 inches by 14 inches and 5 inches deep. In these are solutions for hand and breast cleansing, sponges, and a limited supply of clean diapers for use by the mother. (Soiled diapers are placed in a water proof bag attached to the mother's bed and removed at suitable intervals.) One or the other drawer is close to the mother's reach whether the cabinet is attached to the left or right side of her bed. (See Figs. 1 and 2.)

On the bed rail is bolted a flat rod in which a slot is cut. Two eye blocks are attached to a metal lath through the above slot into which is dropped a hook fastened to the corners of the cabinet. These hooks cannot be detached except by lifting them from the eye. The cabinet in this position can be moved toward the head or the foot of the bed for convenient reach by the mother.

From the George Washington University Hospital, Washington, D.C.
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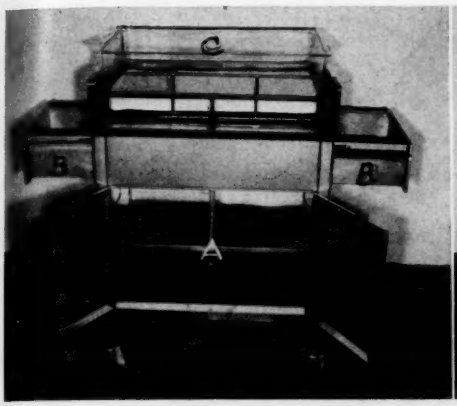

FIG. 1

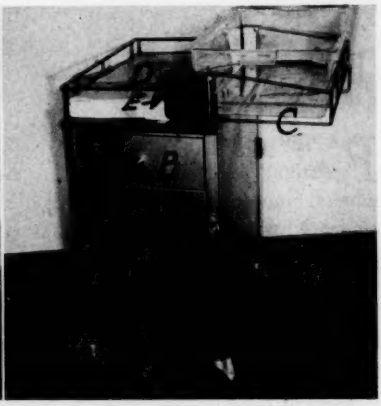

FIG. 2

FIG. 1. A. Linen shelves. B. Utility drawer (right and left). C. Plastic bassinet with pad.
FIG. 2. A. Hook for bed attachment. B. Drawer. C. Bassinet position when over bed. D. Bassinet pad on cabinet top for nurse procedures. E. Mechanism for bassinet movement.

The bassinet is 14½ inches wide, 26½ inches long and 7½ inches deep and made of clear plastic with rolled hand-holds at either end. All corners are curved and the bottom perforated. Cleansing is easily done after discharge of the infant or when it is soiled. The mattress is sponge rubber, 1 inch thick, covered by a rubber casing which is easily removable. The reduced depth of the bassinet allows for easy reach of the infant while the sides are high enough for infant protection.

ACKNOWLEDGMENT

Acknowledgment is made to the engineers of the Simmons Company for putting ideas of the authors into practical mechanical use.

SPANISH ABSTRACT

Gabinete de Lado de Cama para el Recién Nacido Diseñado para Facilidades "Rooming-In"

Al adoptar el principio de "rooming-in" (guardar al niño en el mismo cuarto con la madre) y procedimientos de alimentación selectiva, es necesario proveer un vehículo de infante que haga apropiados y convenientes los métodos del manejo del infante. La cuna en uso en el servicio de maternidad del Hospital de la Universidad George Washington se diseñó para llenar las siguientes necesidades: 1. simplicidad; 2. facilidad en la limpieza; 3. movilidad; 4. compartimientos para guardar el equipo de cuna suficiente para el cuidado completo del infante; 5. accesorio de unión de seguridad a la cama de la madre en posiciones regulables; 6. cuna movible en la parte superior del gabinete para levantar, sacar y volver a colocar al infante con facilidad; 7. cuna de materia plástica clara para observación del infante por la enfermera y la madre.

923 23rd Street, N.W.

BRONCHOGENIC CYSTS OF THE MEDIASTINUM

By L. MARTIN HARDY, M.D.
Chicago, Ill.

RAPID progress in the improvement of procedures in the field of chest surgery has stimulated greater interest in the early diagnosis and treatment of mediastinal tumors. Since many of the mediastinal tumors are of congenital origin and have a definite tendency toward malignant degeneration, they are of particular interest to the pediatrician.

A review of the literature on bronchogenic cysts of the mediastinum reveals that 82 cases[1-16] have been reported, all but three in adults.

Wyllie[7] reported the case of a child, 18 months old, who had a bronchogenic cyst of the mediastinum. This patient died before operation was performed. Tucker[10] reported the case of a 3 month old infant who was not relieved by tracheotomy and died. Autopsy revealed a bronchogenic cyst compressing the trachea and left main bronchus. Maier[16] reported the case of a 9 month old infant who had a large mass which occupied most of the left chest. It was attached to the mediastinum by a small pedicle which ended blindly and was not in close association with the rest of the tracheobronchial tree. The cyst was removed and the baby made an uneventful recovery.

Fifty-three of the 82 patients were operated upon, with 49 recorded recoveries. All of the patients treated surgically were 18 years of age or older except for the 9 month old infant reported by Maier. The cyst in this instance was not within the mediastinum but attached to it by a pedicle.

The paucity of reports of successful operation on congenital bronchogenic cysts of the mediastinum in infants and children prompted this report. A brief summary of the symptoms and diagnostic methods are presented in order to focus attention on the possibility of such conditions in children. Early recognition and removal of bronchogenic cysts will eliminate later complications.

CASE REPORT

D. S., a white male infant 8 mos. old, had a history of a nonproductive cough since birth, at times associated with hoarseness and some dyspnea. He was a full term first born infant who weighed 3.7 kg. Past history and family history were negative. Physical examination revealed a well nourished 9.4 kg. infant who was happy and alert. There was a rather harsh brassy cough. There were increased resonance and distant decreased breath sounds over the left chest posteriorly and inferiorly and some dullness and decreased breath sounds in the left axilla. Inspiratory and expiratory wheezes were present over the entire left chest. Fluoroscopically the left chest remained somewhat areated on expiration, and on inspiration the mediastinum shifted slightly to the left.

The child was admitted to the hospital where the following data were obtained: Mantoux tuberculin test in dilution up to 1/100—negative; histoplasmin test negative; RBC count 4.2 million; WBC count 5.8 thousand; Hgb. 11.5 gm./100 cc.; differential—polymorphonuclears 36%, lymphocytes 64%; urine—trace of albumin, negative sugar and 8-10 white blood cells; repeat urines at later dates were negative; Kahn—negative.

Roentgenologic study of the chest on inspiration showed some shift of the mediastinum to the left, with some relative hyperaeration of the left lung. Anteroposterior and lateral views with lipiodol in the esophagus showed it deviating markedly to the right and posteriorly. Opaque oil in the bronchial tree displayed the right main bronchus clearly but stopped abruptly on the left just

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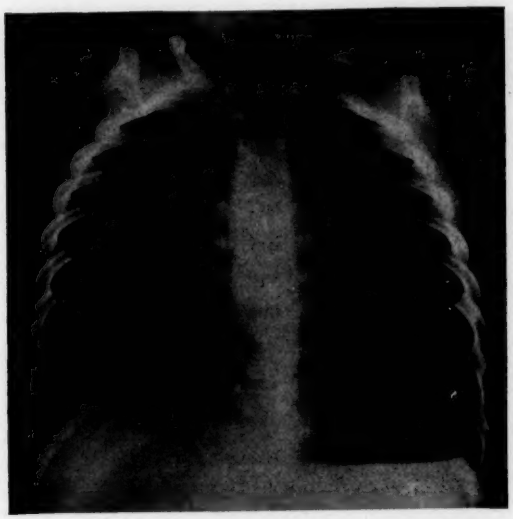

FIG. 1. A-P roentgenogram of chest; hyperaeration of left lung and diamond-shaped mass of increased density in mediastinum.

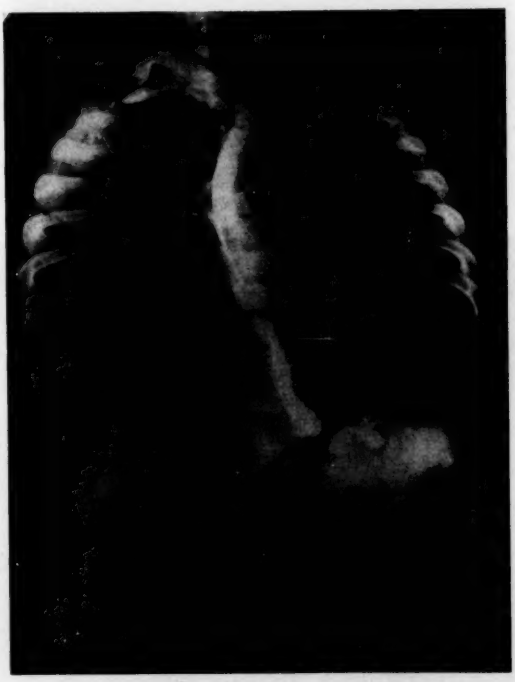

FIG. 2. Esophagram, with chest in A-P position; deviation of esophagus to right.

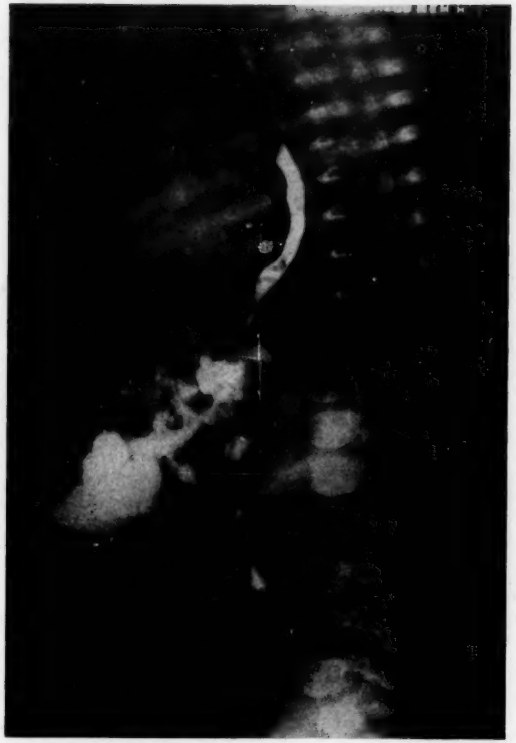

FIG. 3. Esophagram, with chest in lateral position; posterior displacement of esophagus.

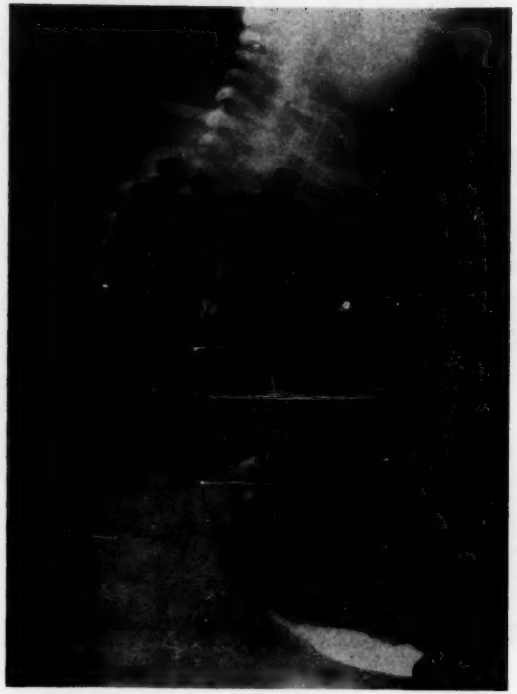

FIG. 4. Broncho-esophagram, with chest in left oblique position; obstruction of left main bronchus and posterior displacement of esophagus.

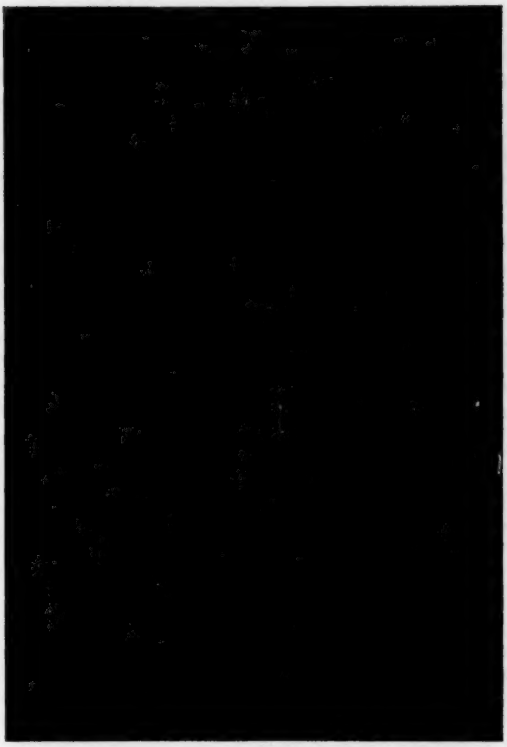

FIG. 5. Broncho-esophagram, with chest in right oblique position; posterior displacement of esophagus and anterior position of trachea.

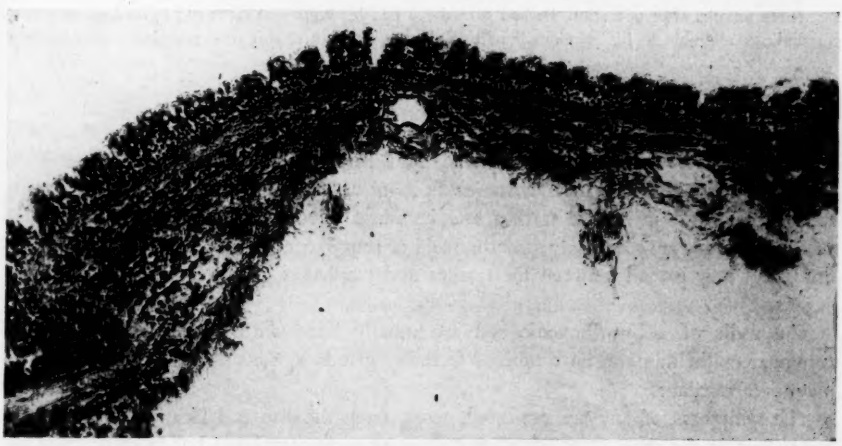

FIG. 6. Photomicrograph of section of cyst wall.

above the bifurcation of the main stem bronchus. There seemed to be an elliptical object of tissue density, measuring approximately 2.5 cm. by 6 cm., which was producing pressure on the esophagus and left main bronchus (Figures 1-5).

Bronchoscopic examination revealed compression of the trachea posteriorly with some occlusion and reddening of the mucosa of the left bronchus. Examination of the esophagus demonstrated a shift to the right, with some compression of the anterior wall. Bronchial aspiration culture showed Staph. aureus hemolyticus and Str. viridans. Ziehl-Neelsen smear and culture of bronchial aspirations gave no acid-fast organisms. A guinea pig was inoculated and showed no evidence of tuberculosis.

Patient developed an upper respiratory infection with a temperature of 38.8° C. from which he recovered in about 6 days. It was decided to discharge the patient from the hospital following this infection and re-examine him at a later date to see if there were any changes in the mediastinal tumor.

He was readmitted 4 wks. later with an upper respiratory infection and temperature of 40.0° C.; he recovered in 4 days and was discharged. He was readmitted 6 days later, again with a cold, and it was decided to keep the child in the hospital and prepare him for operation, since contact with upper respiratory infection was unavoidable at home. The chest findings and the tumor size remained the same. Consequently, in the absence of any active infection, operation was performed in 10 days, by Dr. Willis J. Potts. The following is his operative note:

> The chest was opened at the left interspace. The lung was collapsed and pushed down and dissection in the mediastinal space immediately above the arch of the aorta revealed a cystic mass. The cystic structure was approximately 5 cm. long and 2.5 cm. wide. The entire tumor was dissected free except for a small area in the region of the left bronchus just beyond the bifurcation. There was a hole in the bronchus at least 5 mm. long. It seemed that the cyst sprang from the bronchus and was indirectly attached at its wall. This opening in the bronchus was closed. The child's condition at the close of operation was good.

The postoperative course was uneventful with breath sounds coming in well over the left chest the following day. The cry was strong, color good, and no retractions were evident. The patient was discharged weighing 9.4 kg. and in excellent condition. Roentgenogram at this time showed no mediastinal shift, no air in the chest and slight clouding about the right hilar area.

The specimen removed, a gray white cystic structure, kidney bean-shaped, measured 52 × 25 × 22 mm. in its greatest dimensions. It was air-containing and appeared to be multilocular. Microscopic sections (Figure 6) revealed the largest cavity to be lined with pseudostratified columnar epithelium which in places appeared to have cilia. Subjacent to these were a number of inflammatory cells predominantly of the round cell type. Other cavities were definitely dilated bronchi with mucous glands and plates of cartilage in the walls. These were lined with pseudostratified epithelium. Diagnosis: multilocular cyst of the left main bronchus; bronchogenic.

Three months after operation, he had gained 1.4 kg., his voice was clear and he had no symptoms or findings referable to his previous condition. Roentgenogram at this time revealed a normal chest.

Comment

Bronchogenic cysts are generally considered congenital structures, formed by the pinching off of a small bud or diverticulum of the foregut. They are frequently found in the posterior mediastinum or the posterior portion of the superior mediastinum, usually near the bifurcation of the trachea and occasionally communicating with the bronchi or trachea. They are commonly smooth, ovoid or round, containing a clear, thick, jelly-like fluid, and may extend between the trachea and esophagus, producing pressure on these organs.

The walls of a bronchogenic cyst are usually lined with ciliated pseudostratified columnar epithelium and have mucous secreting glands in the submucous tissue and also plaques of cartilage.

The symptoms, if any are produced, result from the size and location of the tumor mass. Pain in the chest or epigastrium may be an early complaint, but in small children, cough, dyspnea and dysphagia are commonly noted. If the cyst is infected and communicates with the bronchus, expectoration of foul sputum or hemoptysis may be evident.

The findings on physical examination of the chest will reflect to some extent the

degree and location of the mechanical pressure produced on any of the main airways. Bronchoscopy and esophagoscopy rule out intrinsic lesions in these structures and will corroborate the roentgenologic studies regarding the extent of compression and deviation. Roentgenologic and fluoroscopic examinations in the anteroposterior and oblique positions plus broncho-esophagrams are probably the greatest aid. If there are no adhesions the production of a pneumothorax will show the mass in the mediastinum. Also, if the pleural reflexion can be demonstrated onto the mass it suggests that the tumor may be within the mediastinum.[8]

Dermoid cysts and teratomas are usually lobulated. Dermoids are frequently in the anterior mediastinum and occasionally show calcification. Neurogenic tumors are frequently smooth but may produce erosion of the ribs. Malignant tumors cannot be definitely differentiated from the benign by examination alone. They should be suspected, however, when the tumor is diminished in size following roentgen treatment.

With the high incidence of malignancy and the possiblility of malignant degeneration in benign mediastinal tumors, plus the comparative safety of present day thoracic surgery, operative removal seems advisable when a tumor is demonstrated.

Summary

The successful removal of a bronchogenic cyst of the mediastinum in a 10 month old infant is recorded. The character, symptoms, methods of diagnosis and treatment of bronchogenic cysts are discussed.

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Spanish Abstract

Quistes Bronquiogénicos del Mediastino

Se presenta el relato de un caso de un varoncito de 10 meses de edad con un quiste bronquiogénico entre el esófago y la tráquea y pegado al bronquio izquierdo principal. El quiste fué removido con mucho éxito y el paciente se restableció completamente.

700 North Michigan Avenue

AN EVALUATION OF ELECTROENCEPHALOGRAPHY IN THE DIAGNOSIS OF BRAIN TUMORS OF CHILDREN

By JOHN F. DRUMHELLER, M.D., HADDOW M. KEITH, M.D., AND REGINALD G. BICKFORD, M.D.
Rochester, Minn.

IT IS well established that electroencephalography may be used advantageously in locating pathologic lesions of the cerebral cortex through the intact skull. Localization of deep-lying midline brain tumors and tumors of the posterior fossa, however, was originally believed to be impossible by means of the electroencephalogram. Since the incidence of deep-lying midline tumors of the brain and tumors of the posterior fossa is considerably greater in children than in adults, it appeared that electroencephalography would be of little value in the localization of brain tumors of the majority of children.

Smith, Walter and Laidlaw[1] found abnormal, slow waves in the EEG recorded from the posterior portion of the heads of patients having neoplasms of the posterior fossa. These abnormal waves were more pronounced in tracings from the scalp overlying the occipital lobes. They suggested that the abnormal waves were the result of damage to the occipital lobes produced by upward pressure exerted by the lesions through the tentorium.

Walter[2] and Holland[3] reported similar findings in the EEG recorded from patients who had cerebellar neoplasms.

However, Rheinberger and Davidoff[4] and Cobb[5] were unable to find these abnormal waves in the EEG recorded from the occipital regions of patients who had tumors of the posterior fossa. The patients whom they studied were chiefly adults and those studied by Smith and associates and Walter and Holland were children. Rheinberger and Davidoff concluded that the divergence of findings was due to the age factor.

Walter and Dovey,[6] by means of the automatic frequency analysis of brain potentials, found what they concluded was a characteristic rhythm of subcortical tumors. This was a rhythm of approximately 6 cycles per second recorded from the parietal regions.

If the observations of Walter and Dovey and the demonstration of abnormal rhythms over the occipital lobes produced by tumors of the posterior fossa in children are proved to be consistent findings, electroencephalography should be of value in the diagnosis of brain tumors in children.

To evaluate better the status of electroencephalography in the diagnosis of brain tumors of children, a study was made of 50 consecutive case records of children whose ages ranged from less than one year to 14 years. In these cases the diagnosis of brain tumor had been confirmed by operation or at necropsy and EEG had been made before operation.

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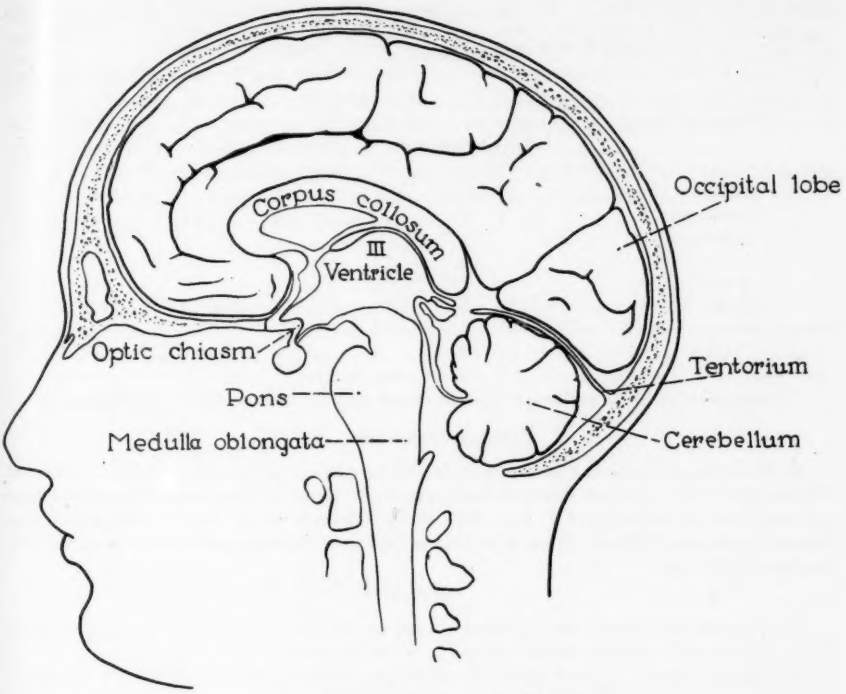

FIG. 1. Medial sagittal section of brain.

ANATOMY

The tentorium cerebelli divides the cranial cavity into the supratentorial and the infratentorial spaces (Fig. 1). The infratentorial space is synonymous with the posterior fossa. Deep-lying midline brain tumors are located in or contiguous to the brain stem. The brain stem is made up of medulla oblongata, pons, mesencephalon and basal ganglia.

TECHNIC

Electroencephalographic tracings were made by a four-channel Grass balanced amplifier and an ink writer which recorded on a paper tape moving at the rate of 30 mm./sec.

The electrodes were fastened to the scalp as illustrated in Fig. 2. Recordings were made by bipolar technic.

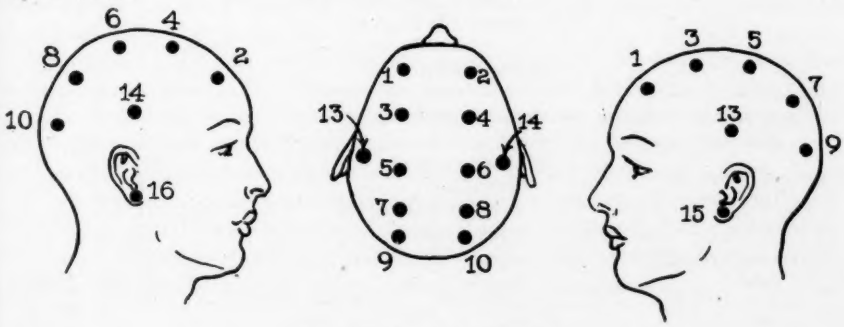

FIG. 2. Placement of electrodes.

TABLE I

OCCURRENCE OF VARIOUS TYPES OF BRAIN TUMORS IN CHILDREN*

Pathologic Types	Location		Total
	Supratentorium	Infratentorium	
Glioma	11	29	40
Sarcoma	4	0	4
Pinealoma	2	0	2
Meningioma	2	0	2
Adamantinoma	1	0	1
Cyst	0	1	1
Total	20	30	50

* This classification of the pathologic types was made with the assistance of Dr. J. W. Kernohan.

CRITERIA OF ABNORMALITY

In this report no attempt has been made to describe the EEG according to any detailed classification. Waves which had a frequency slower or faster than the frequency of normal alpha waves for a given age,[7] and had an amplitude of at least 50% of the amplitude of the normal alpha waves, were considered abnormal. Waves of any amplitude of abnormal frequency which were localized were considered abnormal.

RESULTS

Thirty patients had tumors in the posterior fossa, and 20 had tumors in the supratentorial space. Eight of the supratentorial tumors were situated in or contiguous to the brain stem.

The pathologic types of brain tumors found and the frequency of occurrence in the 2 chambers of the cranium are given in Table I.

In 9 of the 12 patients who had cortical tumors (Table II) abnormal slow waves in the EEG were localized or stronger in the leads from the scalp overlying the lobe involved by the tumor. In 2 patients the abnormal waves were strongest in the record from the scalp overlying the lobe next to that involved by the tumor and on the same side of the midline. The EEG of 1 patient

TABLE II

ELECTROENCEPHALOGRAPHIC FINDINGS IN 20 SUPRATENTORIAL BRAIN TUMORS OF CHILDREN

Site of Tumor	Electroencephalographic Findings	Cases	
Cerebral hemispheres	Unilateral abnormalities		11
	Localized or stronger over lobe involved	9	
	Next to lobe involved	2	
	Bilateral abnormalities		1
Brain stem or contiguous areas (supratentorial)	Unilateral abnormalities		1
	Bilateral abnormalities		7
	Generalized	5	
	Occipitoparietal regions	1	
	Occipital regions	1	
Total			20

showed a generalized abnormality. In this tracing the waves were, however, slower in the tracing recorded from the side of the head containing the tumor. This latter type of record, although not helpful in locating the lobe involved, does suggest the presence of a lesion of the brain and also suggests which hemisphere is involved.

In the 8 patients having deep-lying, midline, supratentorial tumors located in or contiguous to the brain stem no localizing or consistent pattern was observed in the EEG (Table II). The characteristic theta rhythm reported by Walter and Dovey was not observed.

The data on electroencephalograms of the 30 patients who had posterior fossa tumors have been grouped according to whether the abnormal waves occurred in the tracing taken from both sides of the head or from only 1 side (Table III).

TABLE III

ELECTROENCEPHALOGRAPHIC FINDINGS IN 30 TUMORS OF POSTERIOR FOSSA OF CHILDREN

Electroencephalographic Findings	Cases	
Unilateral abnormality		2
Occipital region	1	
Occipitotemporal region	1	
Bilateral abnormality		28
Generalized	5	
Stronger in occipital region	5	
Occipital region	5	
Occipitotemporal or occipitoparietal region	7	
Occipitoparietotemporal region	4	
Parietotemporal region	1	
Parietal region	1	
Total		30

Five patients had generalized bilateral abnormalities in their EEG, 2 had localized abnormalities in their tracings in a region other than the occipital, and 2 had unilateral abnormalities in their EEG. In the electroencephalograms of the remaining 21 patients, bilateral abnormality in the tracing from the occipital region or occipital and contiguous regions was observed. It is this latter type of abnormality that was observed by Smith and associates; an example is shown in Fig. 3.

COMMENT

The value of electroencephalography in the localization of cortical tumors in children is equal to that in adults. In this study a correct localization of the cortical tumors was obtained in 75% of the cases. Since cortical tumors comprise only about 25% of the brain tumors in children, the main problem is to evaluate the use of electroencephalography in the remaining 75% of the cases.

Twenty-one (70%) of the 30 patients having tumors in the posterior fossa had bilateral abnormalities in the EEG recorded from the occipital or occipital and contiguous regions. If this finding is to be used as a diagnostic criterion, it is necessary to consider what other conditions may cause a similar electroencephalographic pattern.

Abnormal electroencephalograms are found in 85 to 95% of cases of epilepsy. However, the occurrence of abnormal waves in the EEG which are stronger or localized in the leads taken from the scalp overlying the occipital region is infrequent. In a recent study by one of the authors (J.F.D.), it was found that electroencephalograms of only 12 of the 169 patients suffering from epilepsy contained such an abnormality.

Gibbs and Gibbs[8] criticized Smith's criterion for localization of tumors of the posterior fossa because it does not differentiate infratentorial lesions from lesions situated in the occipital lobes. This is probably a valid criticism. Fortunately, the incidence of tumors of the occipital lobe in children is relatively rare. In older children, other diagnostic aids, such as a study of the visual fields, could be used to help differentiate tumors of the occipital lobe from those of the posterior fossa.

In the EEG of normal children bilateral abnormal waves are occasionally observed in the occipital leads. In a series of 30 normal controls, two patients were found to have abnormal waves in the EEG similar to those observed in the EEG of children who had tumors of the posterior fossa.

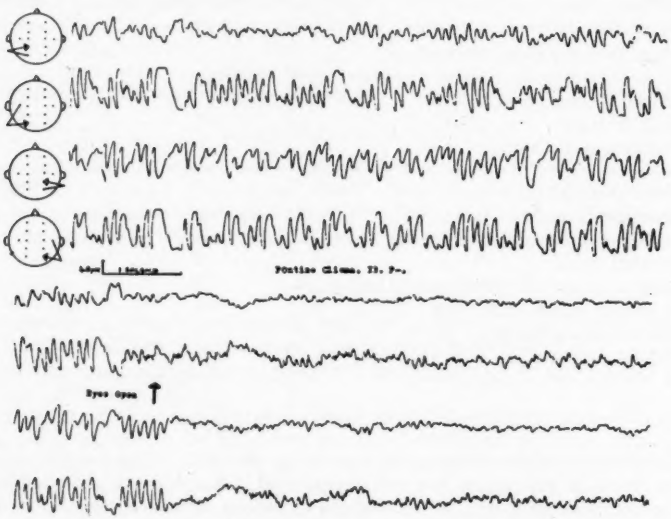

FIG. 3. Abnormal waves in EEG of patient who had brain tumor in posterior fossa.

Dees and Lowenbach[9] studied electroencephalograms from 85 children having allergic disorders. Fifty-two electroencephalograms showed cerebral dysrhythmia, of which 42 were predominantly occipital in type. This occipital dysrhythmia was present in essentially the same proportion in patients suffering from allergy complicated by behavior problems and convulsions as in those children suffering from allergy only.

No attempt will be made to explain the occurrence of the abnormal activity from the occipital lobes as recorded in the EEG of patients who have tumors of the posterior fossa. It has been suggested that the pressure from the posterior fossa against the occipital lobes results in the abnormal electrical activity. The normal brain waves (alpha waves) which arise from the occipital region are usually inhibited when the patient opens his eyes. Smith and associates have suggested that if the abnormal waves arise from the occipital region then they should be uniformly inhibited by direct sensory activation of the occipital lobes. Seven patients who had tumors of the posterior fossa opened their eyes during the recording of the EEG. The abnormality in the EEG of five of these seven patients was decreased by opening of the eyes.

It should be emphasized that in those cases in which the EEG was of no apparent value in the localization of a tumor, it was still abnormal and, hence, was suggestive of some cerebral dysfunction.

Summary and Conclusions

A study was made of the electroencephalograms of 50 children who had proved neoplasms of the brain. In 9 of 12 children who had tumors of the cerebral cortex, the localization afforded by the EEG was correct. In 8 children who had supratentorial tumors of or near the brain stem no localizing or consistent electroencephalographic pattern was observed.

In 21 (70%) of 30 children who had tumors of the posterior fossa a bilateral abnormality was observed in the EEG recorded from the occipital region or occipital and contiguous regions.

It is acknowledged that the abnormality found in this last group also is found occasionally in conditions other than in brain tumors of the posterior fossa. These conditions usually can be excluded by use of the history and other laboratory aids.

Electroencephalography in the study of brain tumors in children should not be considered as an infallible test but rather as a diagnostic aid to be used and evaluated with the help of a clinical history and other diagnostic and laboratory aids.

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Spanish Abstract

Un Avalúo de Electroencefalografía en la Diagnosis de Tumores en el Cerebro de los Niños

Se hizo un estudio de la EEG de 50 niños que tenían neoplasmas del cerebro comprobados. En 9 de los 12 niños que tenían tumores de la corteza cerebral, la localización proporcionada por el electroencefalograma fué correcta. No se observó localización ni patrón electroencefalográfico consistente en 8 niños que tenían tumores supratentoriales en o cerca del tallo del cerebro.

Se observó una anormalidad bilateral en 21 de los 30 niños que tenían tumores en la fosa posterior en los electroencefalogramas hechos desde la region occipital o regiones occipitales y contiguas.

Se admitió que la anormalidad que se encontró en este último grupo también se encuentra a veces en condiciones que no son tumores de cerebro de la fosa posterior. Generalmente estas condiciones pueden ser excluídas por medio del uso de la historia y otras ayudas de laboratorio.

No se debe considerar la electroencefalografía en el estudio de tumores de cerebro en los niños como un ensayo infalible, sino que como una ayuda diagnostica que debe de usarse y avaluarse con la ayuda de una historia clínica y otras ayudas diagnósticas y de laboratorio.

102-110 Second Avenue, S.W.

Pediatrics

VOLUME 4 JULY 1949 NUMBER 1

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

REPORT OF THE EXECUTIVE BOARD MEETING

Atlanta, Ga., April 15-16, 1949

A special meeting of the Executive Board of the American Academy of Pediatrics was held at the Atlanta-Biltmore Hotel, Atlanta, Ga., at 8:00 p.m., Friday evening, April 15, 1949. The meeting was called to order by the President, Dr. Warren R. Sisson. There were present Drs. Sisson, Shaw, Beaven, Barba, Stringfield, McElhenney, Bost, Martmer, London, Wishropp, and Hurtado. Dr. Munns was present on Saturday only. Also in attendance were Drs. Wall, Hubbard and Pease.

Motion was made, seconded and carried that the Academy pay for the badges for the Second Pan-American Congress of Pediatrics meeting in Mexico City (1000 badges at 35 cents each) and also pay the expenses of Mrs. Bundy while in residence at Mexico City and her transportation so that she might take charge of registration from the United States and Canada.

Motion was made, seconded and carried that the additiona! expenses of the President and Secretary of the Academy in attending the Second Pan-American Congress be paid by the Academy.

Motion was made, seconded and carried that Dr. Hugh McCulloch be authorized to open a bank account for PEDIATRICS in the name of the Academy.

Motion was made, seconded and carried that the Committee on Contact Infections be requested to report to the Executive Board in June an outline of the revisions they wish to make in the "Child Health Record" and that the Committee be advised that it is the Board's suggestion that the trend of the revisions be toward simplification.

Motion was made, seconded and carried that the decision as to reprinting the "Child Health Record" up to 5000 copies be left to the discretion of the Executive Secretary.

Dr. Martmer outlined the tentative program for the San Francisco convention in November and suggested that a letter be sent to each member of the Academy asking him to submit a paper for the program, and that the Program Committee and the Editorial Board select from those papers the papers to be presented at the convention. This suggestion was adopted.

Motion was made, seconded and carried that the round tables be limited to one assistant leader and that the expenses of the assistant leader not be paid.

Motion was made, seconded and carried that cancellations of round table reservations be accepted not later than 15 days before the meeting. It was decided that round table tickets not reserved by members prior to the meeting shall be available to members and nonmembers alike on a "first come, first served" basis at the meeting. It was also suggested that round table reservations not be transferred without the written authority of the purchaser, except that such purchaser may personally give such reservations to a second person, providing he notifies the Secretary or another member of the staff of his intention.

Motion was made, seconded and carried that round table tickets that are paid for should be held at the registration desk whether or not the person who paid for the ticket registers.

Motion was made, seconded and carried that the per diem allowance for anyone appearing on the program will not exceed $15.00, it being understood that this would apply only to the day on which he appeared on the program.

Motion was made, seconded and carried that the allowance for mileage shall not exceed 7½ cents per mile airline distance.

Dr. Hubbard presented the report of the Committee for the Study of Child Health Services, including the financial accounting of the Study prepared by Mrs. Elizabeth Lammie. He then read several resolutions, expressing appreciation to the organizations which had assisted in the Study. Motion was made, seconded and carried that these resolutions be approved. (Resolutions on p. 122.)

Motion was made, seconded and carried that a letter signed by all the members of the Board be sent to Mrs. Elizabeth Lammie, expressing the appreciation of the Board for the work she has done.

Motion was made, seconded and carried that the report of the Study Committee be accepted.

Dr. Barba read the report of the Committee on Publicity and Public Relations, including a report on the dinner held for the announcement of the National Report of the Child Health Survey.

The meeting adjourned at 11:00 p.m. and was called to order at 9:10 a.m., April 16, by the President.

Motion was made, seconded and carried that the action of the Executive Board at the Milwaukee meeting be rescinded, and that all funds returned from the states be allowed to remain in the Study account until the final accounting and disposal of that account is made.

Motion was made, seconded and carried that Dr. Hubbard be authorized to pay banquet expenses from the Study Fund. It was understood that Dr. Hubbard would present a detailed report of assets and liabilities of the Study Fund at the June meeting of the Executive Board.

It was announced that the American Medical Association had appointed on its Liaison Committee to meet with a similar committee from the American Academy of Pediatrics Dr. Walter B. Martin of Norfolk and Drs. Margaret M. Nicholson and Joseph S. Wall of Washington, D.C.

Motion was made, seconded and carried that the special committee appointed by the President to meet with the American Medical Association be dissolved.

Motion was made, seconded and carried that a committee of three be appointed by the President to represent the Academy in meeting with the Liaison Committee of the American Medical Association.

Dr. Hubbard presented a report of the activities of the Committee for Improvement of Child Health during the past few months.

Motion was made, seconded and carried that the project in District III be approved with sympathetic interest but that the local group in District III take full financial responsibility.

Motion was made, seconded and carried that the Academy publish the banquet addresses and that the publication be financed by funds from the Study Account; also that in the publication public credit be given to all the donors to the Study.

Dr. Joseph S. Wall presented the Report of the Committee on Legislation.

Motion was made, seconded and carried that the Executive Board approve Bill S. 522 relating to the establishment of Local Public Health Units.

Motion was made, seconded and carried that Bill S. 904, "to provide for research relating to child life and development; to disseminate information as to the practical application of such research by parents, professional persons, and others; and for other purposes," be approved by the Executive Board.

Bill S. 1411, "to provide for the general welfare by enabling the several states to make more adequate provision for the health of school children through the development of school health services for the prevention, diagnosis, and treatment of physical and mental defects and conditions," was considered.

Motion was made, seconded and carried that the Executive Board of the Academy of Pediatrics, at its meeting in Atlanta, Ga., April 16, 1949, approves in principle S. 1411, to strengthen the scope and quality of school health service; the Executive Board recommends that page 2, line 1, be amended by replacing the period after the word "community" by a comma and inserting thereafter the words, "with special reference to utilizing the service of the family physician." The Executive Board approves 1 (B) of Section 6 (a) providing for "treatment of such children for physical and

mental defects and conditions shown by examinations whenever the parents of such children are unable to provide such treatment." The Executive Board would strongly urge the elimination from Section 6 (a) (1) (C) of part of lines 14 and 15 and 16 on page 7—that the State "may provide for the prevention and treatment of such physical and mental defects and conditions for all school children." The Executive Board of the Academy would point out that so far as part (C) is concerned, it opposes the entrance into the private practice of medicine of both the state and federal governments who are jointly involved for those who are able to provide treatment from their own resources.

Motion was made, seconded and carried that the Executive Board of the American Academy of Pediatrics, meeting in Atlanta on April 16, in regard to S-5 reaffirms its action taken at the Detroit meeting in January, 1946, in opposition to a similar bill before Congress at that time proposing compulsory health insurance, believing that political medicine is not for the best interest of the recipients of medical care.

Motion was made, seconded and carried that the Secretary be empowered to pay $250 for a Soundscriber set for Dr. McCulloch.

It was stated that the Board as a whole felt that the Academy had grown enormously and that it definitely needed reorganization, that a committee should be appointed to submit a plan of reorganization which would take into consideration the centralization of the efforts of the Academy, the functions of the ICH Committee and all the committees, specifying what their duties are and possibly reorganizing the committees, and that some definite plan should be made for the future of the business side of the Academy.

Motion was made, seconded and carried that the currently existing Committee on Reorganization be dissolved with thanks and appreciation.

Motion was made, seconded and carried that the Executive Board be empowered to appoint a new Committee on Reorganization, consisting of two members of the Executive Board, one Past President, the Chairman of the discontinued Committee on Reorganization, one member at large, and the President and the Secretary-Treasurer ex-officio members, this Committee to be charged with the duty of:

(a) Making a thorough and critical study of the existing organization of the Academy, including the headquarters in Evanston, the ICH office in Philadelphia, and the office of PEDIATRICS in Chicago.

(b) Bringing to the Executive Board at its June 1949 meeting recommendations for reorganization of the Academy's executive and administrative offices and functions in keeping with the rapidly expanding responsibilities of the Academy. Any changes in the Constitution called for by the Committee's recommendations should be included in its report to the Executive Board.

That the Committee on Reorganization have authority to draw on the Academy's treasury for necessary expenses up to $1500 for meetings, travel and the services of legal counsel in reviewing the Constitution.

The following members of the Committee were appointed by the President: Dr. Borden S. Veeder (Past President), Chairman; Dr. Philip S. Barba (Executive Board); Dr. Paul Beaven (Executive Board); Dr. James M. Baty (Discontinued Committee on Reorganization); Dr. William Belford (Member at Large).

Motion was made, seconded and carried that the President be instructed to inform the Chairman of the ICH Committee and its Executive Director that it is the Board's feeling that the ICH Committee should be continued and should have the power to raise funds, but that it should be borne in mind that a strict economy program should be instituted in the ICH Committee's office.

Motion was made, seconded and carried that the ICH Committee be requested to submit a budget to the Budget Committee before the June meeting of the Board.

Motion was made, seconded and carried that the elections of State Chairmen be conducted through the District Chairmen unless the State has previously been organized.

The meeting adjourned at 4:50 P.M.

WHEREAS, The Study of Child Health Services and Pediatric Education is now completed and reported, and

WHEREAS, This unprecedented undertaking could not have reached successful completion without

the generous financial support of the National Foundation for Infantile Paralysis, not only in a large grant from its national headquarters but also contributions from its county chapters at the state level, be it

RESOLVED, That the Executive Board of the American Academy of Pediatrics meeting in Atlanta, April 16, expresses in behalf of the fellows of the Academy its sincere appreciation for aid and cooperation received during the conduct of the Study and for its continuing support to the Committee for the Improvement of Child Health, and be it further

RESOLVED, That a copy of this resolution be sent to the President of the National Foundation for Infantile Paralysis, with a request that this expression of the Academy's appreciation be made known to the county chapters.

WHEREAS, The Study of Child Health Services and Pediatric Education is now completed and reported, and

WHEREAS, This unprecedented undertaking could not have reached successful completion without the generous financial support of The Field Foundation, be it

RESOLVED, That the Executive Board of the American Academy of Pediatrics meeting in Atlanta, April 16th, expresses in behalf of the fellows of the Academy its sincere appreciation for the support and cooperation of The Field Foundation received during the conduct of the Study and for its continuing support to the Committee for the Improvement of Child Health, and be it further

RESOLVED, That a copy of this resolution be sent to the President of The Field Foundation.

WHEREAS, The Study of Child Health Services and Pediatric Education is now completed and reported, and

WHEREAS, This unprecedented undertaking has attained new heights of cooperative enterprise between voluntary and official organizations concerned with the health and well being of the children, be it

RESOLVED, That the Executive Board of the American Academy of Pediatrics meeting in Atlanta, April 16th, expresses in behalf of the fellows of the Academy sincere appreciation for the expert personnel and generous financial support contributed to the Study by the U.S. Public Health Service, and be it further

RESOLVED, That particular thanks be expressed to Dr. Leonard Scheele, Surgeon General, to Dr. Thomas Parran, Surgeon General at the time the Study was started, for his prompt and generous support, to Mr. Perrott for his cooperation and assistance on the Advisory Committee and to those members of the U. S. Public Health Service who served as members of the Executive Staff: Dr. Charles L. Williams, Jr., Mrs. Maryland Y. Pennell and Miss Mary Cawley, and be it further

RESOLVED, That a copy of this resolution be sent to the Surgeon General and those named above.

WHEREAS, The Study of Child Health Services and Pediatric Education is now completed and reported, and

WHERAS, This unprecedented undertaking has attained new heights of cooperative enterprise between voluntary and official organizations concerned with the health and well being of the children, be it

RESOLVED, That the Executive Board of the American Academy of Pediatrics meeting in Atlanta, April 16, expresses in behalf of the fellows of the Academy sincere appreciation for the expert personnel and generous financial support contributed to the Study by the U. S. Children's Bureau, and be it further

RESOLVED, That particular thanks be expressed to Dr. Eliot for her cooperation and assistance on the Advisory Committee and to those members of the U. S. Children's Bureau who served as members of the Executive Staff: Dr. Katherine Bain and Mrs. Jean Ellis, and be it further

RESOLVED, That a copy of this resolution be sent to the Chief of the Children's Bureau and to those named above.

WHEREAS, The Study of Child Health Services and Pediatric Education is now completed and reported, and

WHEREAS, This unprecedented undertaking could not have reached successful completion without the generous financial support of Mead Johnson and Company, M & R Dietetic Laboratories, Inc., Carnation Company, Pet Milk Company, Lederle Laboratories Division, American Cyanamid Company, Cutter Laboratories, Mennen Company, Borden Company and National Dairy Products Corporation, be it

RESOLVED, That the Executive Board of the American Academy of Pediatrics meeting in Atlanta, April 16th, expresses in behalf of the fellows of the Academy its sincere appreciation for the support received during the conduct of the Study from those pharmaceutical firms named above, and be it further

RESOLVED, That a copy of this resolution be sent to each of the firms named above.

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309 E. 33rd St.
Baltimore 18, Md.

Dr. Theresa T. Woo
P. O. Box 5523
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The following Fellows of the Academy have died recently:

Dr. George Lindsay Cook
442 W. Lafayette St.
Tampa 6, Fla.
(Died March 9, 1949.)

Dr. John Lyttle
4614 Sunset Blvd.
Los Angeles 27, Calif.
(Died Nov. 26, 1948.)

Dr. Martin G. Neely
301-304 Woodward Bldg.
Birmingham 3, Ala.
(Died April 23, 1948.)

Dr. Worth Ross
351 Farmington Ave.
Hartford 5, Conn.
(Died Nov. 9, 1948.)

Dr. Eugene Rush
1832 Spruce St.
Philadelphia 3, Pa.
(Died Feb. 19, 1949.)

Dr. M. Scherzer
Suite 414, Medical Arts Bldg.
Montreal, Quebec, Canada
(Died Aug. 12, 1948.)

Dr. Lillian R. Smith
Hardwich
Barnstable County, Mass.
(Died April 13, 1949.)

Dr. Frederick F. Tisdall
55 College St.
Toronto 2, Ontario, Canada
(Died April 23, 1949.)

Dr. Abraham M. Litvak
1145 Eastern Parkway
Brooklyn 13, N.Y.
(Died Jan. 28, 1949.)

Pediatrics

VOLUME 4 JULY 1949 NUMBER 1

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy

REFLECTIONS, PROTESTATIONS AND SUGGESTIONS OF A MEMBER OF THE LOYAL OPPOSITION

By HUGH J. MORGAN, M.D., F.A.C.P., D.Sc.

IT IS a pleasure and a great honor to come to the Old North State from a daughter state, Tennessee, to speak to you on the occasion of the 150th anniversary of the foundation of your Medical Society.

The conventional address for such an occasion would be a historical one. Certainly, old records of this Society provide extraordinarily rich and attractive material for the historian. Your current program of medical education, medical research and medical administration in relation to the improvement and extension of medical care, both preventive and curative, is a source of pride and stimulation for all of the southern states. North Carolina is leading the way in the South.

But I do not plan to review in detail the past or current accomplishments of the profession in North Carolina. This has just been done for us in a scholarly and inspiring address by Dr. Hubert A. Royster. Suffice it to say that the membership of your Society has exhibited a capacity, unusual in organized medicine, for self examination and self evaluation and has been alert to change. Your membership has been judged courageous and progressive, and the country in general and the South in particular has become accustomed to look to North Carolina for guidance and example. Perhaps some of you hardly

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Dr. Morgan is Professor of Medicine at the Vanderbilt University School of Medicine, Nashville, Tenn.

Read at the Sesquicentennial Celebration of the Founding of the Medical Society of the State of North Carolina, Pinehurst, N.C., May 10, 1949.

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recognize yourselves as I talk! Maybe there are a few of you like the thieving, prowling, lying and intemperate colored man on judgment day who read, as he arose from his grave at the sound of the trump, the inscription on a tombstone—provided by the faithful, generous wife who survived him—"Here lies an honest man, a faithful husband, a truthful citizen and a temperate, devoted churchman." "Scuze me, Lord," said our friend, "I done come up outer the wrong grave!"

I propose to talk tonight not so much of the past as of the present of medicine. There are developments of great moment taking place, developments of lasting influence upon practice as we have known it. We think of the past 30 years as the golden age of therapeutics and well we may when we list such achievements as the mastery of many of the anemias, of diabetes, of deficiency diseases, and of heretofore little understood metabolic and endocrine disturbances both in the male and the female, of modern anesthesiology, neurologic, thoracic and vascular surgery, malaria control, replacement therapy with blood and blood derivatives, and most amazing of all—the contemplation of which still reduces us to incredulity and humble thanksgiving—modern chemotherapy. The sulfonamides and the antibiotic medicaments have not only increased tremendously the effectiveness of medical treatment—they have changed the whole atmosphere of practice. Compare our position now with that of 15 years ago when confronted with bacterial infections such as puerperal sepsis, septicemia, meningitis, endocarditis, pneumonia, peritonitis, urinary tract infections and tuberculosis. And now (1949) we dare believe that we can influence specifically certain of the rickettsial and viral diseases; that we can specifically and regularly induce remissions in rheumatoid arthritis! No sane man in 1935 would have allowed imagination to raise his hopes to such heights. Today the physician disputes with the surgeon his claim to maximum effectiveness as a practitioner. We look upon internal medicine as the most progressive and most effective and most adequate branch of therapeutics. No longer do nonsurgical practitioners get satisfaction solely from scientific and philosophic contemplation. We are effective, successful therapists, aggressive and unapologetic! And, as a sort of extra dividend, the methods and technics and therapeutic agents of internal medicine have extended tremendously the domain of the surgeon. Together, students of the broad disciplines of internal medicine and its specialties, including pediatrics, and of surgery and its specialties, including gynecology and obstetrics, are attaining successes never before experienced by practitioners of the healing art in all the long history of man's effort to cure disease and relieve suffering. I cite this golden age of therapeutics as the product of basic and clinical research and of enlightened medical practice. Never was therapeutics so effective as today, and never was the future for additional progress brighter.

But this isn't all that has happened in medicine in the recent past. Not only has there been tremendous activity and accomplishment in research and in practice but there have also occurred great changes in medical economics and in the attitude of the public toward the doctor and his mission. I propose to direct your attention to certain aspects of these changes. I ask that you think about them simply and honestly and with relation to your own professional life in your community. Let me reassure you at this point. Already I have talked seven minutes. I don't propose to spend the remaining 25 minutes of my address in an effort to analyze socio-economic changes, to study the background of them, to point out the present manifestations of them or to indicate possible future developments with relation to them. To do this requires knowledge and wisdom and time which I do not possess. I can recognize some of the factors currently influencing health and health

services and the attitude of the public toward them: the tremendous increase in the effectiveness of medical services; the industrialization of our country; the extension of our urban culture into rural areas; improved communication and efficient, rapid transportation; steady elevation of the educational level and of the standard of living of the population. Perhaps there are others. All have in my lifetime operated to create a population alert and anxious for improvement and advantage over previous generations, a population unafraid of experimentation and change. (Indeed, one gets the impression that in the minds of many, change and newness in themselves constitute a virtue. And what is strange about this in a bewildered, desperate world which in three decades has fought two wars and now talks pessimistically about a third, final, atomic war?) However this may be, it is my contention, and a major premise of my reasoning, that the victories and achievements of medical science and the scientific doctor, and other factors, have created an informed population which demands and insists upon medical services of quality and quantity heretofore unknown to them. This demand will not and should not be denied.

And so we are doctors in a rapidly changing world. How would our forebears of the Medical Society of the State of North Carolina have conducted themselves today if they had been confronted with the threat of federalization of medical services in the United States? More important still, what have we, the living, functioning professional men of today, what have we to say about it? Our country is making desperate efforts abroad at international readjustment to the end of avoiding another armed conflict and at home is faced with the necessity of constant adjustment and readjustment to political and social forces, some of which seem completely alien to many of us. To be specific with relation to domestic problems, what position is the doctor to take with regard to the labor movement and with regard to the development of health services within the labor movement; with regard to the extension of the public health movement with its steady encroachment upon the private practitioner; with regard to group practice; with regard to schemes of coordinated medical practice developed around central laboratories and central integrated hospitals and medical centers; with regard to prepayment schemes for the provision of medical services which tend to fix fees and to that extent impersonalize economic arrangements of practice; with regard to the use of public monies or taxes to support medical education and medical research; with regard to the concept that medical care both preventive and curative should be as available as pure water, that it is the responsibility of government to see that its people have this necessity just as it is the responsibility of government to see that its people have proper personnel and facilities for education, transportation, communication, police and fire protection. How do we physicians react to these questions?

A subsidy of some sort is involved in many of these questions. Subsidy is not a very popular word in certain quarters. But consider this fact: Only a very small percentage of the population can pay its way when confronted with serious illness. Shouldn't we find the best way to subsidize medical services to the end that all "our people actually enjoy the good health that medical science knows how to provide?" Shouldn't we subsidize all of the indigent sick in order that they be able to share the advantages of "the golden age of therapeutics?" Otherwise many will die for the lack of modern life-saving remedies. Perhaps this violates principles dear to the hearts of some of us—is contrary to the rugged individualism of the so-called American way of life. Let me remind you that some of those who howl the loudest for "free enterprise" and a competitive economy are themselves beneficiaries of governmental and private philanthropic largess. Our govern-

ment at one time or another has subsidized railroad, shipping, the air lines and the farmer; it protects American business against foreign competition; it provides free education; it exempts religious worship from taxation; it assists veterans with G-I bills and pensions. Here is subsidy, indeed, and on a wide front. One step more before abandoning this line of thought. Very few men in this room paid their way through college and fewer still through medical school. Medical education costs four to eight times the tuition fees. If we subsidize medical students in amounts four to eight times greater than their contribution to their education in order that they may become doctors, is it inconsistent or immoral or un-American to subsidize the sick in order that they may obtain what these same doctors have to offer? Of course it is not! The only question warranting serious consideration is "how" to do it and, at the same time, to sustain our standards of citizenship on the one hand and medical practice on the other.

It seems to me that the doctor has two roles to play in this life and that he should play them both with great respect for his fellowman and also with great self respect. The first and by far the most important role is that of the professional man whose major concern is the practice of the art and science of medicine to the end of preventing, alleviating or curing disease and injury. This is his primary mission, his destiny. His life is dedicated to this end, and beyond providing a decent living for self and family, he is basically unconcerned with the economic or social setting. The second role is that of the citizen, an informed and educated citizen who, being a professional man with special training, has special insights and special knowledge and whose judgment, therefore, should be of a special value to his fellow. Of course, the doctor must be concerned with political, social and economic problems and he must take position and even provide leadership with relation to them. But here he must be careful because he is who he is and because his primary mission in life is what it is. How important it is that he play this citizen-role unselfishly, high-mindedly, and with the maximum good of the people he ministers to always his first consideration. Moreover, he must condition himself to accept the judgment of the people with relation to social and economic matters and not let his own judgment relative to them warp or change him or mitigate against his ability and effectiveness in his primary role as physician. Whatever may be the economic, social and political setting provided him, he must always remain the professional man. His answers to the perplexing question of what he thinks about the public health movement; private practice; group practice; hospital centers; prepayment schemes; socialized medicine—his answers must rest on professional considerations first, economic and political considerations last. In the final analysis, his answers are based on what the matter under consideration does to the quality and quantity and distribution of medical services and not upon how it will affect his pocketbook or his political party affiliations.

I quote here from an address to the American College of Physicians:[1]

"What is a profession? The word is derived from the Latin 'professio' which means 'open declaration; public avowal; claim, as of a religious faith and purpose.' It is defined as 'a calling in which one professes to have acquired some special knowledge used by way either of instructing, advising or guiding others or of serving them in some art.' The word 'calling' is used in the above definition, and it in turn deserves clarification. It is defined, perhaps with an element of mysticism, as 'a divine summons, or prompting to a particular act or duty.'

"Theology, the Law, and Medicine are generally referred to as the three learned

professions. They are to be sharply distinguished from Business which 'applies especially to occupations of a mercantile nature' and Trade which 'applies to any of the mechanical employments or handicrafts except those connected with agriculture.'

"Dr. Vannevar Bush's[2] concept of a profession, as revealed to a group of engineers and recorded in his book of essays called 'Endless Horizons,' represents the thoughts of a great scientist, a hard-bitten realist, an extraordinary administrator, patriot and one of America's foremost professional men. Dr. Bush emphasizes and reemphasizes the point that the core of a profession is 'ministration to the people.' The initial and central theme of every one of the professions is that they minister to the people. Ministry is more than just service. It offers no apology and is not subservient. It is characterized by authority based on knowledge. Authority in Medicine implies great responsibility. It follows that dignity and prestige are accorded by the people to those providing this ministration."

I do not pretend to know the answers to the problems this country is wrestling with in relation to medical services, medical research and medical education. But there are a few observations and comments I wish to make about them. The people want more and better medical care. Most people want it for all the people, whether all the people can pay for it or not. The President's stated objective to extend optimum medical care to just as many people as can be reached with our personnel and facilities is also the objective of the vast majority of people of the United States. This is a fact. The people not only want this, but they and their representatives in government are determined to have it if it can be gotten by passing laws. I am wholly sympathetic with the President's objective. My disagreement with him has to do with ways and means only—and I believe this is the way doctors in general feel. Certainly this is the way most of them act in their daily work for I do not know of any other group of people who provide charity services in equal quantity.

Let us look at medical services in the United States and decide how good or how poor they are and how abundant or how scarce they are. I am not going to bore you with a recital of Mr. Ewing's vital statistics showing how many people in the United States have no medical services to speak of—or, at best, only emergency medical services, and these of a very poor quality. There is exaggeration—but there is also truth in what he says. Nor am I going to grind the foundation stones of your patience into a fine powder by expounding and expanding upon the American Medical Association's slogan that under the free enterprise system we've got the best health record and the best medical services of any country of any world in any universe at any time!

Let us agree to this and start with the premise that we've got the best there is—this is a good, popular fourth of July position to take, and in North Carolina we can say that this position has the backing of 100 years of active, effective organized medicine and 50 additional years of maturation. However, the really important question is: are we as doctors satisfied with what we have? Without further ado, let us state that neither the truly professionally minded among the producers (the doctors) nor the consumers (the public) are satisfied. Let us thank God that neither we nor they are anesthetized by an attitude of complacency and satisfaction with the status quo, a "God's in His heaven and all's right with the world" point of view. The latter quotation, it seems to me, usually means that the world in question is no larger than the very limited horizons of the individual contemplating it. It would be better said: "All's right with my world," not "All's right with God's world." As Dr. William MacNider would say, "God should be

allowed to speak for Himself." So we'll say that in our country medical services are good and that they need to be better; they need to be more abundant; more widely distributed; less expensive.

How to accomplish all this? Under a free enterprise system? Under a socialistic system?

I'm sure I don't know, but I do know that there has been an awful lot of loose talk about the principle of "free enterprise" in medicine and also about "socialized medicine." A few words about the latter. I take it that socialized medicine is medicine under complete government control—the levels of authority being federal, state, county and municipal. Actually, we know a good deal about socialized medicine already. The Medical Departments of the Army, Navy, Air Force, Public Health Service and Veterans Administration are socialized with authority and control operating at the federal level. Our state, county and municipal institutions are socialized at the local levels. There are 1,425,000 hospital beds in the United States. Half are for general care; the other half for long term chronic diseases. Almost all the long term or chronic illness beds (tuberculosis and mental diseases) and about half the general hospital beds are being operated by government. State and local governments operate 830,000 and the federal government 200,000 beds. Thus, less than 400,000 of the 1,425,000 beds in the United States are operating under the free enterprise, voluntary system.

The federal government is attempting to give varying degrees of medical care to 24,000,000 beneficiaries—about one sixth of the population of this nation. Veterans estimated to number 18,500,000 constitute the bulk of this large group. This one sixth constitutes federal government operation in the field of medical care. Our states have taken over the tuberculosis and mental health problems pretty nearly completely. I dare not estimate how much of the whole this segment of medical services for the population comes to, but add it to the services provided the 24,000,000 federal beneficiaries and add also services for the huge population whose health is the responsibility of city and county government agencies. When you add all these beneficiaries of government health services together, you have a startlingly reduced number of the population left to be cared for under the private enterprise system, by private practitioners and voluntary health agencies. Actually, the practicing physician is cooperating extensively with or without remuneration in federal, state, county and especially municipally administered socialized medicine.

Is this socialized medicine as we see it, and have seen it for years, so pernicious in principle and of such poor quality as to be altogether condemned? Certainly not! I would say that Army, Navy, Air Forces and Veterans Administration medicine is good over-all —and far better in 1949 than that practiced in the average home or hospital throughout the country. Perhaps you will not agree with me. I make the statement advisedly and on the basis of fairly extensive observation. What about the effect of working in such a system of socialized medicine upon the doctor? What happens when the factor of competition is sharply curtailed; when the operation of the profit motive is abolished or greatly diminished? I don't think anything much happens if professional standards are safeguarded. I don't put the preservation of "the private enterprise" principle in medicine before the preservation of the professional principle in medicine. I believe it is infinitely more important that doctors continue their ministration to the people than that private enterprise be preserved in medicine. What has happened to the doctor of medicine whose

concept is so rigid and narrow as to preclude ministration to the people except under the capitalistic system in an atmosphere of free enterprise and competition? What has happened is that he has ceased to be a professional man and has become an economist or a business man. I am sick of hearing our professional leaders insist and reinsist ad nauseum upon the "preservation of the private enterprise system in medicine" as though this economic principle was indeed an ethical, moral or professional matter. It would appear that for these doctors the economics of medicine comes first and overshadows completely the professional concept, the sole "raison d'être" of the practitioner: ministration to the people. Let us not take the tradesman's view. To be opposed to socialized medicine because it would impersonalize and degrade the practice of medicine through the development of a huge federal governmental hierarchy with central control of medical services; because it would propose to provide services which simply can't be provided in the United States at this time with our personnel and facilities—and the attempt would surely lower professional standards in many areas; because the tradition of our country is to sponsor individual initiative and performance rather than regimentation; because it would defeat the healthier, more natural, time-honored approach to the improvement of medical services through nongovernmental, voluntary arrangements; to disapprove socialized medicine for such reasons as these is one thing. To be intemperate, illogical, inaccurate, selfishly materialistic and misinformed is another—and it behooves the members of a learned profession to mark well this point. Socialized medicine will lower the ethical standards, ideals and moral values of individual doctors? Do you really believe that? As for myself, I don't! Some of the most high-minded, intelligent and effective men of medicine I know have been in the past or are now presently working in socialized medicine and every medical scientist worth the title has long since turned his back upon private enterprise and the profit motive. Let us oppose socialized medicine, if we do oppose it, for valid reasons—not because of stupid maxims, mottoes and slogans.

What about health insurance? The people want it and are going to have it. They know that for the low income group modern medicine is too expensive to be provided any other way. They want a broad policy covering medical as well as surgical illnesses and the coverage must be country-wide. Such insurance should be made available on a voluntary basis to people of all income levels. Government should provide the premiums for the indigent so that they, too, may be covered. The only form of health insurance I would like to see made compulsory is that paid for by government for the indigent. Why organized medicine refused to work out a national insurance scheme under the Blue Cross, Blue Shield plan as proposed by Paul Hawley last summer is beyond my understanding. It isn't too late to do it now. If the American Medical Association or some other agency doesn't do it, I am confident that Mr. Ewing's program of compulsory health insurance will be inaugurated. The people are determined to have health insurance. The question, it seems to me, is merely whether it will be government insurance with federal bureaucracy or private insurance. While I strongly favor the latter and have spent a great deal of time and some money working for it and against Mr. Ewing, I would vote for Mr. Ewing's plan unless a better one is offered. You see, I, too, want insurance with broad coverage and reasonable rates.

Before I conclude this discussion, let us get down to cases. What should be our position, as physicians, before the people in these critical days? What do we stand for? What do we want and how do we get it? Let us consider these questions in terms of our primary

role in life. Let us be professional in our approach, not economic and political. We want, within the limits imposed by the availability of personnel and facilities, to extend optimum medical care to the maximum number of people. We recognize that more personnel and more facilities are needed. Moreover, more money is needed than most citizens have to pay for medical care. How shall we get what we want? I believe that the American Medical Association should become the champion of a movement to improve and extend medical care in the United States and this because the American Medical Association, a professional society, recognizes, indeed, insists that medical care in the United States should be improved and extended! It, the American Medical Association, should reclaim its position of leadership before the people by emphasizing its professional responsibilities and opportunities, and by ceasing to advocate merely the preservation of the status quo. It should, in association with the American Public Health Association, the American Hospital Association, welfare organizations and other representatives of the people, evolve a positive, comprehensive National Health Plan—a plan to improve and extend medical care which will be so manifestly advantageous to the public and physicians alike that it will be acceptable in preference to any other. This, and not mere opposition to Ewing or to Murray, Wagner and Dingle, is the role for us to play as members of organized medicine. This is the way for us to reclaim prestige due us as professional men in medicine. Most important of all, this is the way for us to help the people of this country obtain more and better medical service—to help our people experience the enormous benefits and advantages of living in this golden age of therapeutics. What an opportunity is ours! What a goal to achieve! This, indeed, is ministration to the people and in the finest tradition of one of the noblest professions it is man's privilege to espouse.

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TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

ON MAY 11 and 12, the Sub-Committee on Health Legislation of the Committee on Labor and Public Welfare held hearings on S. 904, a bill to provide for research relating to child life and development. As previously reported in this column, this bill proposes to provide $7,500,000 for the first year, and as much thereafter as may be necessary, for research relating to child life and development. This bill would broaden the mandate of the Children's Bureau to investigate and report upon all matters pertaining to the welfare of children and child life.

The chief emphasis of the bill is on integrated research calling for a multiprofessional approach, including the biologic, medical, psychologic, physical and social aspects of child life and development, as well as the community aspects of child life. Funds would be made available to disseminate information as to the practical application of new knowledge related to the health and well being of children; to make grants to universities and other public and private agencies for research projects; to establish and maintain research fellowships for qualified research specialists; to "provide training and instruction and establish and maintain traineeships in child life and development and pediatrics." A National Advisory Council of 15 members would advise the Children's Bureau in running this program, and would recommend research projects and programs.

During the two day hearings on this bill the following witnesses appeared: Senator Douglas, who introduced the bill; Donald Kingsley, Assistant Administrator of the F.S.A.; Dr. Martha Eliot, Associate Chief of the Children's Bureau; Dr. Leonard Scheele, Surgeon-General of the Public Health Services; John Gardner, Carnegie Corporation, New York; Dr. Robert Sears, Child Welfare Research Institute, University of Iowa; Philip E. Rettig, National Society for Crippled Children and Adults; George Hecht, American Parents' Committee; Dr. Benjamin Spock, Rochester Child Research Clinic; Lawrence Frank, Caroline Zachary Institute of Human Development; Alfred Marrow, Harwood Manufacturing Company; W. B. Schoembohm, Crippled Children's Home, Jamestown, North Dakota; Dr. Joseph Wall, American Academy of Pediatrics; Dr. John Gillin, Professor of Anthropology, University of North Carolina.

The testimony presented for the American Academy of Pediatrics by the undersigned Chairman of the Committee on Legislation was as follows:

The Executive Board of the American Academy of Pediatrics, meeting in Atlanta, Ga., on April 16, 1949, and acting for the Academy during the interim between annual meetings, unanimously approved S. 904, the National Child Research Act and urged its passage by the Congress.

The organic Act, passed by the 62nd Congress in 1912, which established the Children's Bureau, reads in part: That said Bureau shall investigate and report . . . upon all matters pertaining to the welfare of children and child life among all classes of our people, and shall especially investigate the questions of infant mortality, the birth rate, orphanages, juvenile courts, desertion, dangerous occupations, accidents and diseases of children, employment and legislation affecting children in the several States and Territories. It will be noted that the Bureau was originally established to *investigate and report,* but as the years passed, more and larger functions of administration and of service were added by various Acts of the Congress to its duties, which have, to a certain extent, overshadowed and eclipsed the burdens originally assigned to it by the basic Act.

Briefly, the expanding functions of the Bureau by direction of the Congress have included the administration of the Child-Labor Laws, of the Federal Maternity and Infancy Act in effect from 1922 to 1929, popularly known as the Sheppard-Towner Act, of Title V of the Social Security Act of 1935 concerned with maternal and child welfare and crippled children, and finally of the Emergency Maternal and Infant Care Act which prevailed during the years of World War II, providing medical and hospital care for thousands of the families of enlisted men in our armed forces.

It is thus apparent that the functions of administration and of service have to a large extent overshadowed the basic concepts of the Congress as to the duties of the Bureau in regard to research, investigation and report, a situation which evolved because of the increased burdens assigned to the Children's Bureau through legislation.

It is our belief that the enactment of S. 904 would augment and implement the basic purposes intended by the Congress in the organic Act of 1912, and would remove certain restrictions now inherent in the legislation establishing the Bureau, in that the National Child Research Act will permit research in the field, as directed in Section 3, (a) to "conduct, assist, and foster INTEGRATED research and demonstrations relating to child life and development," and further, in Section 3, (f), (A) and (B), "establish and maintain research fellowships in the Bureau AND ELSEWHERE," and "provide training and instruction and establish and maintain traineeships in child life and development and pediatrics in the Bureau and in medical and other schools and institutions providing instruction in medical social and related aspects of child care and development."

Assuredly, growth and development of children cannot be observed and studied from behind desks in the Federal buildings in Washington, but such research must be carried out in the environment of the child, in the home, the school, in the clinic and in the hospital. The Act permits such field studies and the integration of the efforts of the Children's Bureau with public and private centers of investigation into the problems of growth and development of children.

In evidence of the success which can be expected through integration and cooperation by the Children's Bureau with other public and private agencies, we would submit for the information of the committee the report just published of a Study of Child Health Services and Pediatric Education conducted by the American Academy of Pediatrics in cooperation with the U. S. Public Health Service and the Children's Bureau.

Comment

After the testimony of the witnesses, who had then left the stand and resumed their seats, the Chairman, Senator Murray, asked if they had seen a copy of the amend-

ments suggested by the Administrator of the Federal Security Agency and if such amendments would have influenced their views on S. 904. An assistant then presented to them the amended copy of the bill which had in its format the appearance of the original bill but carried the suggested amendments and eliminations proposed by the Federal Security Administrator, as well as a legend in large type, "CONFIDENTIAL COMMITTEE PRINT."

Several witnesses were recalled and vigorously expressed their opposition to the proposed amendments which, in their opinion, would serve to weaken the Act and lead to administrative difficulties.

The gist of the amendments proposed was to give increased authority to the Administrator (of Federal Security) and to reduce substantially the influence and powers of the National Advisory Council, as well as to limit its numbers to 12 instead of 15.

In several sections of the bill such phrases as "in cooperation with the Advisory Council" were made to read "in consultation with," while in Section 3, in four paragraphs, the word "recommendation" (by the Advisory Council) has been stricken out and replaced by the word "consultation."

From those witnesses given the opportunity to reiterate their views came unanimous opposition to the proposed amendments, especially to those taking away from the Advisory Council the power to recommend grants-in-aid and to recommend the establishment of fellowships.

JOSEPH S. WALL, M.D., *Chairman*
Committee on Legislation

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

NURSES CONSIDER PLANS FOR NEW ORGANIZATIONS

By HORTENSE HILBERT, R.N.

(Chairman, Committee on Structure of National Nursing Organizations; Director, Public Health Nursing Service, New York City Department of Health.)

THE effort to coordinate nursing organizations in the United States and make them more effective in the tremendous task of meeting the nation's constantly increasing demand for nursing care, which has become known among nurses as "the structure study," is currently being given fresh impetus as nurses all over the country hold workshops to consider two new plans prepared by their Committee on the Structure of National Nursing Organizations.

The study of the structure of organized nursing began more than a decade ago when the board of directors of the American Nurses' Association, in response to a recommendation of a state nurses' association, voted that a special committee be appointed to consider the possibility of consolidating the American Nurses' Association, the National League of Nursing Education, and the National Organization for Public Health Nursing.

Next definite action occurred in January 1944, when the boards of directors of those three organizations voted to undertake a joint survey of their "organization structure, administration, functions and facilities to determine whether a more effective means can be found to promote and carry forward the strongest possible program for professional nursing and nurses." A committee representative of all three organizations was formed, and in late 1944 and early 1945 representatives were named to the committee by three other organizations, the National Association of Colored Graduate Nurses, the American Association of Industrial Nurses, and the Association of Collegiate Schools of Nursing.

In April 1946 this committee representing six national nursing organizations employed the Raymond Rich Associates to conduct a study. A preliminary report from the study was presented before the biennial convention of ANA, NLNE, and NOPHN at Atlantic City in September 1946 and published under the title of "Report on the Structure of Organized Nursing" (Am. J. Nursing **46**:648, 1946).

Either during the biennial convention or soon thereafter the six organizations elected representatives to an enlarged continuing committee which, with changes in numbers of representatives and a slight name change, continues as the present Committee on Structure.

On the Committee are 60 persons from all over the country. Fifty-seven are nurses and three are non-nurse members of two of the organizations participating in the structure study. Committee members consist of 20 representatives from the ANA and eight each from the other four nursing organizations, including the presidents and executives of all six nursing organizations.

The Committee's aim has been the democratic enlistment of all members of the six

organizations in consideration first of the Raymond Rich plans, and later of proposals by the Committee itself.

The Committee prepared and published for consideration in the spring of 1948 a "Tentative Plan for One National Nursing Organization." This plan proposed a single organization, to be known as the American Nursing Association, with nurse members grouped into sections, and composing the house of delegates and the board of governors. In addition, this single association was to have divisions, which were to have non-nurse, agency and school members as well as nurse members. Only nurse members of the division were to be eligible to election as division representatives in the house of delegates and board of governors, but all types of members were to help elect the division representatives.

The several actions on structure taken at the biennial convention of the ANA, NLNE and NOPHN in Chicago in May and June 1948 seemed to indicate that the nursing profession wanted two things:

1. The uniting of their present organizations into one, which would offer membership to all graduate registered nurses and, in addition, to non-nurses, schools of nursing, and nursing services.

2. Continued membership in the International Council of Nurses (known as the ICN).

The two aims seem to be incompatible, at least for the time being. The International Council's Constitution states that members shall be "one national association from each country, composed of nurses or a national federation of nurses," yet since non-nurses were to have limited representation in the proposed organization, its admissibility seemed to be a question of interpretation that only the ICN itself could answer. The question was brought before the Board of Directors of the ICN at their London meeting in September 1948 and, in light of fears of interference from outside the profession expressed by nurses from some countries, it was decided not to press for a decision at this time.

Major difference between the two 1949 plans now under consideration is the method proposed for that cooperation with consumers of nursing and members of allied professions in the health field which nurses have sought more directly than have most professional groups. Two of the organizations participating in the structure study, the National Organization for Public Health Nursing and the National League of Nursing Education, have traditionally sought this cooperation through including non-nurses among their members. For example, pediatricians have often sat on standing committees of the former group.

One of the new plans proposes to amalgamate the present six organizations into two, with a joint board to coordinate their activities. One of these organizations, a new American Nurses' Association, would have only professional nurses as members. The second organization, the Nursing League of America, would include among its members nurses, non-nurses, schools of nursing and the nursing services in hospitals, public health agencies and industries.

The other plan is for one organization, the American Nursing Association, which would have only registered nurses as voting members. The Association would, however, set up discussion forums to which nurses, non-nurses, schools of nursing and the various types of nursing services might belong. Such forums would have advisory powers only in relation to the Association.

Proposals as to how nurses would work together on professional problems are similiar in both plans. Both meet in the same way—through setting up sections and councils of specialists—that question which puzzles nearly all professional organizations, how to give sufficient autonomy to the various groups within the profession to serve their specialized needs and at the same time to preserve unity in the organization as a whole. For example, it is proposed that nurses qualified in pediatric nursing compose a council to work for advancement of standards in that field.

The sections to which all members of the professional association would belong by individual choice would serve as the basis for proportional representation of the occupational groups in the house of delegates and on the board of governors, as well as carrying on considerable activity of their own.

Both plans suggest that all members of the professional association attending a biennial convention constitute an assembly to provide a voice at national meetings for any member, whether or not a delegate. It is also proposed to institute the system of choosing a president-elect of the nurses' association to assure a two year training period for anyone chosen to leadership of professional nurses in the United States.

It is proposed that members of the Nursing League of America in the two organization plan be grouped into divisions and departments to serve the special needs of various types of members. An important function of the League's national headquarters, as indicated in the proposals, would be to provide counseling to schools of nursing and nursing services in the adjustments which rapid expansion of health services are requiring. Boards of directors of the six existing organizations were unanimous in voting to place the two plans before the profession for consideration.

The board of directors of the American Nurses' Association favored the one-organization plan since members, at two meetings of that Association's House of Delegates, have indicated their interest in one national nursing organization.

Boards of directors of the other five organizations favored the two-organization plan for reasons that may be stated in part as follows:

1. Nurses and their public need organization machinery through which they may work actively together toward the betterment of nursing services. The need is particularly great just now when plans of both voluntary and governmental agencies for expansion in all fields of health services point to major changes both in schools of nursing and in nursing services. Nurses must and will have their all-professional organization through which to work on all matters of concern to a professional group, and this professional organization must be as deeply concerned with the service needs and resources of the community as it is with the welfare of the individual members. At the same time, it is important to offer non-nurses voting memberships in an organization to achieve the desired cooperation.

2. It is not possible for a single corporation to engage in a legislative program that involves lobbying in the interests of organization members and at the same time to receive contributions which the donors may deduct for income tax purposes. It would obviously be important for a nurses' organization to be free to work for or against any legislation, whether national, state or local, that it wished. At the same time, gifts from foundations and others will be essential to an on-going program in nursing.

3. Another aspect of the incorporation question is the fact that the education and service part of a national nursing organization should be able to look to nursing agencies

for increasing support. Most voluntary public health services and many hospitals receive Community Chest funds. It is essential that any national organization expecting to receive dues from agencies which, in turn, receive support from Community Chest funds should establish tax-free status.

4. To continue the help now being provided by existing organizations to nursing services and to schools of nursing, and to extend that help as required to maintain and build up standards during the era of change that doubtless lies ahead, it is essential to continue to offer membership to agencies and schools. This requirement involves (a) the need for an organization with a tax-free status as discussed just above and (b) the possibility of offering voting memberships to the many non-nurses as well as nurses who compose boards, faculties and staffs of such agencies and schools.

NEWS AND ANNOUNCEMENTS

The National Foundation for Infantile Paralysis has awarded postgraduate fellowships in the fields of scientific research, physical medicine and public health.

Three of the new fellows will devote their time to research projects in the field of pediatrics. Dr. John J. Osborn, of Larchmont, N.Y., has already begun his project at New York University—Bellevue Medical Center under Drs. L. Emmett Holt, Jr., Professor of Pediatrics, and Colin MacLeod, Professor of Microbiology; Dr. Paul Harold Hardy, Jr., of Baltimore, Md., and Dr. David I. Schrum, of Houston, Texas, will start their work July 1, respectively, at Johns Hopkins Hospital, under Drs. Francis F. Schwentker, Pediatrician-in-Chief, and Horace L. Hodes, Associate Professor of Pediatrics; and at Louisiana State University School of Medicine under Drs. Myron E. Wegman, Professor of Pediatrics, and G. John Buddingh, Professor of Microbiology.

These fellowship awards of the National Foundation for Infantile Paralysis are financed out of current appropriations of $340,000 March of Dimes funds and are in addition to National Foundation grants of $740,000 administered since 1940 through the National Research Council.

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A study is being made in the Department of Pharmacology and Toxicology of the University of Rochester School of Medicine and Dentistry, under the direction of Dr. Harold Hodge, to determine to what extent the effects of therapeutic drugs and exposure to toxic chemicals contribute to the high death and disability rates due to accidents.

This study is part of a wider consideration of the medical aspects of accident control, and is concerned particularly with the problem of injuries and poisonings which occur in homes and on farms. There is special emphasis on the etiology of accidents to children between the ages of 1 and 20 years, since accidents are the leading cause of death in this age group, and second only to congenital malformations as a cause of permanent disability.

In dealing with industrial and traffic accidents, some degree of mechanical and legal control is possible. In homes and on farms, where the accident rate is highest, the most authoritive influence is that of the practicing physician.

It has been shown statistically that about 20% of the total population have most of the accidents. There is also considerable evidence to show that many of these accident-prone individuals are suffering from physical or emotional disorders which can be diagnosed and treated clinically. The baffling problem of accident control may well find its solution in the offices of the private practitioner.

A request is therefore being made to pediatricians to help in the study described above. The immediate need is for case histories of the following type:

1. Records of patients who have had accidents while under the effects of medication, such as antihistaminics, anticonvulsants, barbiturates, sulfa drugs, insulin, bromide, atropine and novocaine.

2. Records of patients who have had accidents after exposure to toxic chemicals, such as carbon tetrachloride and naphtha.

3 Records of patients who have suffered kidney or liver damage after exposure to toxic chemicals. There is special interest in case histories of such damage after exposure to carbon tetrachloride used for dry cleaning, as a solvent, or as a water-mark detector by stamp collectors.

4. Records of patients who have had repeated small or major injuries because of some physical disorder, such as limited hearing, defective vision, orthopedic impairment, epilepsy (slight petit mal or psychomotor attacks), heart failure and diabetes.

Assistance in obtaining this material will be greatly appreciated. Please address all communications to: Marion Gleason, Research Assistant, Department of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry, Rochester 7, N.Y.

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Course in Allergy for Clinicians

October 1949 to October 1950

Objectives: The primary purpose of the course is to give physicians an understanding of those conditions which are usually classified as allergic. The course emphasizes clinical aspects and also

endeavors to give a well-rounded theoretical background on which clinical knowledge is built.

The course in allergy is accredited for 1 year towards the formal training requirements of either the American Board of Internal Medicine or of the American Board of Dermatology and Syphilology. Enrollment is limited to 10 students.

For further information, write to University of Illinois Allergy Unit, Colleges of Medicine and Pharmacy, 1853 W. Polk St., Chicago 12, Ill.

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THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS, 120 BROADWAY, NEW YORK 5, N.Y.

SHORT COURSES IN THE DIAGNOSIS AND TREATMENT OF POLIOMYELITIS PATIENTS FOR PHYSICIANS SCHEDULED DURING 1949

(As of May 1, 1949)

Training Center	Scheduled Courses	For detailed information and for enrollment write to:
Children's Hospital, Boston, Mass.	June 13-17 Aug. 15-19	William T. Green, M.D.
City Hospital, Cleveland, Ohio	July 18-23 Aug. 8-13 Aug. 29-Sept. 3	John A. Toomey, M.D. Dept. of Contagious Diseases
D. T. Watson School of Physical Therapy Leetsdale, Pa.	1-3 weeks, depending on need of each individual. Dates to be specially arranged. Emphasis on when to prescribe the respirator and when the rocking bed, with variations to meet the needs of each patient.	Jessie Wright, M.D. Medical Director
Georgia Warm Springs Foundation Warm Springs, Ga.	3-6 months, starting July 5, and October 3.	Robert L. Bennett, M.D. Director of Physical Medicine
Stanford University School of Medicine San Francisco, Calif.	3 days—probably the second week in July.	W. H. Northway, M.D. Assistant Dean
University of Colorado Denver, Colo.	May 23-28 Nov. 14-19	Winona C. Campbell, M.D. Director of Poliomyelitis Teaching Program

* * *

Diplomates certified by the American Board of Pediatrics after examinations at Baltimore, Md.—May 7, 8 and 9, 1949:

Antell, Gunnard John, 310 Coral Way, Coral Gables, Fla.
Bandi, Robert Thomas, 901-4 Central Union Bldg., Wheeling, W.Va.
Barmeyer, George H., The Western Montana Clinic, Missoula, Mont.
Bashinsky, Leo M., 2028 Highland Ave., Birmingham 5, Ala.
Buchbinder, Selma, 74 N. Village Ave., Rockville Center, N.Y.
Clayton, Edgar L., 3 Aldin Lane, Levittown, Hicksville, N.Y.
Crigler, John Fielding, Jr., Harriet Lane Home, Baltimore 5, Md.
Cunningham, George F., 615 Third St., Brooklyn, N.Y.
Davens, Edward, 2411 N. Charles St., Baltimore 18, Md.
Debuskey, Matthew, 2412 Eutaw Pl., Baltimore, Md.
Dent, John Henry, Tulane University of Louisiana, New Orleans, La.
Dolgin, Joseph, 33 Central Ave., St. George, Staten Island, N.Y.
Dormont, Richard Edward, Louisiana State University, New Orleans 13, La.
Dunn, S. Chester, 227 W. Kleberg, Kingsville, Tex.
Elston, Anny, 242 E. 15th St., New York 3, N.Y.
Golden, Theodore S., 118 Union Ave., Framingham, Mass.

Gruber, Seymour, 640 Eastern Pkwy., Brooklyn 13, N.Y.
Guild, Harriet Griggs, Johns Hopkins Hospital, Baltimore 5, Md.
Hardy, Janet Baillie, Johns Hopkins Hospital, Baltimore 5, Md.
Hardy, Paul Harold, Jr., Johns Hopkins Hospital, Baltimore 5, Md.
Hodes, Horace L., Sydenham Hospital, Baltimore, Md.
Kajdi, Laslo, Johns Hopkins Hospital, Baltimore 5, Md.
Keller, Maurice J., 101 Federal St., Salem, Mass.
Klugherz, Marjorie B., 2100 Avenue J., Brooklyn 10, N.Y.
Laski, Bernard, Hospital for Sick Children, 67 College St., Toronto, Canada.
Lecks, Harold I., 5701 Ogontz Ave., Philadelphia, Pa.
Linson, Elizabeth Sarah, 214 N. Potomac St., Hagerstown, Md.
Lysaught, James Neill, Johns Hopkins Hospital, Baltimore 5, Md.
Markowitz, Milton, Johns Hopkins Hospital, Baltimore 5, Md.
McMackin, Lillian Francis, 71 Blue Hill Pkwy., Milton, Mass.
Metcoff, Jack, 300 Longwood Ave., Boston, Mass.
Mosher, Thomas Edward, 525 E. 68th St., New York 21, N.Y.
Nestor, John Oliver, 2170 N. Glebe Rd., Arlington, Va.
Rider, Thomas Lewis, 959 Washington Ave., Albany, N.Y.
Rothman, Martin, 91 Emerson St., Haverhill, Mass.
Rubin, Justin, 5927 Pine St., Philadelphia 43, Pa.
Russell, Marie Esther, 583 Haddon Ave., Collingswood, N.J.
Sawan, Edward A., 797½ N. Main St., Akron, Ohio
Schaffer, Alexander J., 8 E. Eager St., Baltimore 2, Md.
Schwentker, Francis F., Johns Hopkins Hospital, Baltimore 5, Md.
Silver, Francis F., 9400 Euclid Ave., Cleveland 6, Ohio
Spence, George Roland, 904 Ellsworth Dr., Silver Spring, Md.
Spragins, Melchijah, 102 Alleghany Ave., Towson, Baltimore 4, Md.
Stewart, Frank Ashbrook, 34 Bull St., Newport, R.I.
Stewart, James B., 12900 Euclid Ave., East Cleveland, Ohio
Stone, Ethon L., 143 N. Jackson St., Jackson, Mich.
Taussig, Helen B., Johns Hopkins Hospital, Baltimore 5, Md.
Taylor, Grant, Duke Hospital, Durham, N.C.
Temple, William Joseph, 1 Wallace Ave., Covington, Ky.
Trevett, Elizabeth Peabody, 240 Prince George St., Annapolis, Md.
Unna, Maya Stromberg, 23 W. Calendar Ave., La Grange, Ill.

BOOK REVIEWS

ORAL VACCINES AND IMMUNIZATION BY OTHER UNUSUAL ROUTES, David Thomson, O.B.E., M.B., Ch.B., D.P.H., and Robert Thomson, M.B., Ch.P., assisted by James Todd Morrison, M.D., D.P.H. (published for the Pickett-Thomson Research Laboratory, London), Baltimore, Md., Williams and Wilkins Company, 1948, $11.00, 329 pp.

This is interesting reading. It is amazing how many attempts have been made to induce active immunity against bacterial and viral diseases by introducing antigen via the intestinal, pulmonary, nasal, oral and dermal routes. A tremendous number of reports, some critical and many otherwise, have been reviewed by the authors. They include studies of their own on immunization against colds. A large body of evidence is here collected showing that under certain conditions, and in certain species, artificial immunity of varying degrees may be conferred by employing these unorthodox routes.

The oral administration of typhoid vaccine, originally with the intent to produce local immunity of the intestinal tract and later to produce general immunity, has been used extensively in Italy, Rumania, Russia, South Africa and Japan. It is difficult to escape the conclusion that ingested typhoid vaccine confers a degree of protection. When studies were properly controlled, statistically significant protection has occasionally been demonstrated. However, the conclusion of the authors that this method "is just as, if not more, efficient than the subcutaneous method" is certainly not shared by other authorities.

In the case of BCG vaccine, the oral route, of course, was the original one employed by Calmette and Guérin. But it was not until the intradermal route was used that fairly convincing evidence of protection was obtained in Denmark, in Chicago and on American Indian reservations. No public health official now would contemplate a return to the original oral route.

The dubious value of orally administered bacillary dysentery and cholera vaccines has become of historical interest only. Active immunization against dysentery is impractical because of the multiplicity of strains. Cholera vaccine given by the subcutaneous route, however, has finally been accepted by most authorities. Oral immunization against colds with mixed vaccines composed of respiratory pathogens (and nonpathogens) failed when subjected to careful scrutiny.

Inhalation of antigens in the form of a fine mist is impractical because of the possibility of inducing asthma. Intranasal instillation of pertussis vaccine exerts a protective effect in laboratory animals (mice) but it has not been effectively evaluated in man. Intranasal instillation of diphtheria toxoid was carefully investigated by Phair in 1942. Whereas he was unable to induce primary immune responses in susceptible adults, he did succeed in provoking effective secondary immune responses in individuals who had experienced previous contact with diphtheria toxin or toxoid. Unfortunately, however, the high incidence of unpleasant local reactions, particularly in individuals sensitive to the intradermal injection of toxoid, makes the method impractical.

Immunization against diphtheria by inunction (the Lowenstein method) is relatively ineffective and transient.

The one promising possibility gleaned from this book is the report of Bousfield on diphtheria toxoid pastilles for reimmunization. When 3 or more pastilles were allowed to dissolve in the mouth daily for 7 consecutive days, rather marked increases in serum antitoxin could be demonstrated. No undesirable reactions occurred. There was no evidence that the pastilles provided adequate stimulus for primary immunization. This work has recently been confirmed in this country by Masucci, Gold, and DeFalco (J. Pediat. **32**:35, 1948). As the reimmunization of toxoid sensitive adolescents and adults presents a practical difficulty in colleges, medical schools and armed forces, any method which may provide an effective secondary stimulus without producing a severe local reaction becomes of great interest. Hence, the truly oral, not intestinal, route for reimmunization against diphtheria stands out as the sole potential procedure of value in this comprehensive review.

THE CHALLENGE OF PARENTHOOD, Rudolph Dreikurs, New York, N.Y., Duell, Sloan & Pearce, Inc., 1948, $3.50, 326 pp.

In this approach to the manifold problems of 20th century parents, Dr. Dreikurs has wisely stressed the constructive aspects of the parental role in child rearing, offering many concrete suggestions for positive action in specific settings. His discussion of mental hygiene principles is couched in language which has meaning to the interested parent, and his treatment of such potentially difficult areas as the setting of limits for aggressive behavior, the sensitive enlightenment of the child on sexual matters, and the handling of minor behavioral deviations by the judicial usage of matter-of-fact and superficial interpretations of the child's partially conscious goals of behavior seem sound and effectively developed. Dr. Dreikurs' psychiatric orientation has its basis in the precepts of Alfred Adler, but his book fortunately avoids the doctrinaire characteristics of many psychologic monographs. The discussion of the employment of group principles in parental treatment and of the observation in a group setting of all sibling members of a family constellation carry more particular interest for the clinician.

As with many books, certain limitations appear to this reviewer to mar the cogency and unified character of Dr. Dreikurs' presentation. Although he has successfully avoided many of the pitfalls open to the recent group of popularizers of psychiatric concepts who attempt to minister in one literary capsule to the needs of several segments of the reading population, the author has included a rather sketchy treatment of unconscious forces and their role in the motivation of human behavior. Some of this apparent over-emphasis on conscious experience in the molding of personality trends stems from the Adlerian belief in the importance for the individual of a drive toward accomplishment and superiority which is based on inferiority feelings arising from an awareness of personal, often physical, limitations. From this approach, too, may result his rather weighted description of the process of education as a response by the child to a series of guided and unguided frustrations with affection toward and identification with the parent or educator as a mechanism of apparently lesser importance. The author's indictment of flexible feeding schedules in his desire to impose from the onset a measure of order and regularity upon the infantile gastrointestinal tract seems somewhat unphysiologic in the light of recent studies by Aldrich, Gesell and others. In general, however, Dr. Dreikurs has produced a monograph which can be of positive influence upon searching and all too frequently confused parents.

VIRUS DISEASES OF MAN, C. E. van Rooyen and A. J. Rhodes, New York, N.Y., Thos. Nelson & Sons, 1948.

With the onset of effective antibiotic and chemotherapy of bacterial infections, viral diseases have come relatively more and more to the fore. As a consequence, tremendous efforts have been made in laboratories the world over to study these infections. The progress made in the past decade can easily be gauged by comparing the new edition of the "van Rooyen and Rhodes" with the original volume. In mere figures, 270 pages have been added and the individual page is larger than in the old edition. Many chapters had to be completely rewritten and new ones added concerning over 20 new virus diseases of man or infections only recently established as caused by viral agents.

The new edition fulfills admirably what the virologist has been hoping for and has needed for a long time. It is an extremely valuable reference book for the worker in this field and it is amazing to realize how even minor details of the vast literature have been noted and included in the discussions. Publications practically up to the date of printing of the new volume, i.e., up to early 1948, are included.

It is not intended, however, to create the impression that this volume is of interest to the specialist only. It contains much practical information for physicians concerned with viral infections such as the pediatrician, internist, neurologist, dermatologist and ophthalmologist. It will be of great value to the epidemiologist and those charged with the care of public health.

The only criticisms which this reviewer can think of, and which actually cannot be taken as such, are a regret that rickettsial diseases are not included and subjected to an equally thorough discussion, and that viral infections of animals likewise are omitted, inasmuch as an increased knowledge of these diseases might well reflect on our understanding of some of the problems facing us in the viral diseases of man. It is obvious that inclusion of these fields would increase the task to such an extent that no two-man team could handle it.

STUTTERING, Charles Van Riper, Ph.D., Chicago 3, Ill., National Society for Crippled Children and Adults, 1948, .30, 60 pp.

No malady, not even epilepsy, has been regarded by the public with more superstition than has stuttering. The well-known diversity of opinions among speech pathologists as to the etiology and therapy of stuttering has been anything but helpful to the layman. Recently the National Society for Crippled Children and Adults asked the American Speech and Hearing Association to prepare a booklet on the subject of stuttering for popular distribution. To Professor Charles Van Riper was assigned the difficult task of preparing a manuscript which would avoid controversies, which could be endorsed by authorities of widely varying schools of thought, and which could at the same time manage to say something concrete and enlightening. To add to the author's difficulties, no fewer than 23 speech pathologists from across the nation were asked to criticize the first draft of the manuscript.

The result of Professor Van Riper's efforts has been far beyond what might have been expected in such a situation. His brief and readable treatise will be most illuminating to anyone interested in stutterers. It should be particularly helpful to parents of stuttering children. The pediatrician can well suggest it to parents, and to nurses, social workers and teachers, as well as his professional colleagues. The booklet makes no pretense of furnishing all the information on stuttering that any of these persons need to know, but it provides an excellent beginning.

YOUR BABY: THE COMPLETE BABY BOOK FOR MOTHERS AND FATHERS, Gladys Denny Shultz and Lee Forrest Hill, M.D., Garden City, N.Y., Doubleday & Company, Inc., 1948, $3.50, 278 pp.

This is a handsome, attractive baby book with many excellent photographs and line drawings. It contains a record section of some 38 pages in addition to the 237 pages in the text. Its aim is to provide the "Complete baby book for mothers and fathers" as a supplement to regular medical care.

There is a great deal of good and accurate information contained in its pages regarding the physical care of the child, including diet and a discussion of some of the more common ailments and accidents, and his physical and emotional development. One is particularly glad to see some advice to the couple concerning the need for antepartal care and the recognition of the father as an important person in the family group.

It is in the area of providing guidance to the parents in understanding the child, admittedly a difficult task, that the book seems to fall short of its commendable goal.

There seems to be some oversimplification in solving certain problems. For example, in regard to breast feeding there is advice given to such problems as diet, rest periods and freedom from worry. The statement is made that serenity of mind is important, and that if a mother makes up her mind to breast feed her baby and follows directions, she will be successful. This is only a part of the truth, however, and would seem to overlook the not inconsiderable number of mothers in our culture who consciously wish to breast feed their babies but are not able to do so in spite of really sincere efforts. Preparation for breast feeding during the antepartum period can be much facilitated by education of the prospective mother on such problems as diet, feeding technics and breast care, and by discussion of what her feelings are about breast feeding. However, one should expect that there will remain some mothers who will fail as breast feeders for unconscious reasons.

The material on emotional development and emotional problems at times shows great understanding of children and the dynamics of their development. Yet at other times there is an inconsistency in what might be called the philosophy of the book. One gets the impression that some of the paragraphs are "inserted" into the text rather than being an integral part of the belief of the authors. To cite a specific example: In the area of feeding, the chapter on the self-regulating schedule is presented in an interesting and readable manner as a method of feeding which the authors endorse. However, elsewhere in the book (chapter 5, page 57) there is the statement, "When your baby cries, look first at the clock." There is advice to "Manipulate a schedule to meet the needs of your child," but also advice that the youngster's schedule should be kept faithfully, and throughout the book there are numerous schedules with stated hours for doing certain things which seem to refute the permissive viewpoint.

Finally, it would seem to this reviewer that this baby book could make a valuable contribution to parents and their children by devoting more time to helping parents understand something more of

the parent-child relationship and the part they play as individuals with their own individual feelings and characteristics. The feelings of parents seem to receive too little elucidation so that one gets the impression that they are expected to be serene, good-humored and even-tempered at all times.

It would seem desirable also if these well-meaning parents could be helped to realize that committing to memory the advice of any book, however good, will not in itself make parenthood easy. They are being bombarded from many sources by books, articles and radio talks on how to rear children. Though in many respects this is good, it also may be confusing. Parents often are threatened by the mountains of printed material they feel bound to read in order to rear their children properly, and frustrated when things do not go as the books say they should. Thus, some of our books, though written with the intention of helping parents, may actually make them less secure and less able to enjoy being "good" parents. They need help, not of the dogmatic but of the supportive type, in order that they may develop a sense of their real importance to the child and that they may grow and mature in their parenthood.

It should be pointed out, and the authors have done this nicely, that guidance to parents can be given only partially in any book and that much help should come from the interpersonal relationship of the family with the physician.

PREMATURE INFANTS: A MANUAL FOR PHYSICIANS, Ethel C. Dunham, M.D., Washington, D.C., The Children's Bureau, 1949, 400 pp.

National statistics show that the single greatest cause of infant deaths is premature birth which accounts for one half of all infant deaths in the first month of life. As pediatricians well know, the tragedy is that many of these infant lives could be saved—if given the specialized care needed. Despite the fact that at least 1 in 20 babies is born prematurely, a great many practitioners have little specialized training in the care of these infants and little knowledge of their particular problem. To help fill this gap in medical knowledge, the Children's Bureau has just published a comprehensive guide for the general practitioner and other professional people. It is *Premature Infants, A Manual for Physicians,* by Ethel C. Dunham. Dr. Dunham is well known to all Academy members. After her long years at the Yale School of Medicine, she became associated with the Children's Bureau where she was Director of its Division of Research in Child Development, until she retired in 1940. Since then she has spent much of her time in compiling this manual.

Running some 400 pages, *Premature Infants* brings together for the first time available information in the literature on premature infants. It treats the subject in 2 main parts: General Considerations and Clinical Considerations. The first part analyzes the objective measures, the incidence, causes and prevention of prematurity, and the growth and development of premature infants. The second part deals with the physical problems and care of premature infants: resuscitation, incubator care, nutritional requirements, congenital malformations, infection and other conditions.

EVERYDAY PROBLEMS OF THE SCHOOL CHILD, Agatha H. Bowley, Ph.D., Edinburgh, Scotland, E. and S. Livingstone, Ltd., 1948, 140 pp.

This volume is addressed to teachers primarily and describes children at different educational levels. The organization of material is unique in that it centers around children grouped according to the British Educational System from the toddlers in the Day Nursery through Nursery School, Infant School, Junior and Secondary Schools.

Dr. Bowley, School Psychologist in Leicester, England, shows sympathetic understanding of children at all ages and discusses their psychologic problems ably. Her down-to-earth understanding is illustrated by illuminating descriptions of behavior problems typical of the 5 different developmental levels covered by the book.

She analyzes a variety of problems from her own experience and suggests practical methods she has found successful in handling them. Quite outstanding is her chapter on the child in the Infant School (ages 5, 6, and 7). Her discussion of educational technics, especially free activity methods and the adjustment class, is worthy of note and full of helpful suggestions.

The book should prove valuable to pediatricians and parents as well as to teachers.